VOLUME II

PRACTICE OF SURGERY

Current review

BALLINGER / DRAPANAS

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Practice of surgery: current review

Volume II

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PRACTICE OF SURGERY

Current review

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With 249 illustrations

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Volume II

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Preface

In Volume I of *Practice of Surgery: Current Review* we stated that we hoped to add a vehicle whereby the interested reader could pick the brains of an authority in the field without spending countless hours in the library culling information from a myriad of sources. We believe that we achieved that goal and hereby offer Volume II to our readers. As in the previous volume, the chapters were culled from a variety of subjects and include not only areas of current interest but also those in which important advances have been made within the last few years.

In Volume II the members of the Departments of Surgery at Tulane University School of Medicine in New Orleans and at Washington University School of Medicine in St. Louis were again called on to present a critical appraisal of a specific subject, including a bibliography. Efforts have again centered on obtaining the concerted opinion of the authors relating to the status of the current work in the field and its application to the care of the surgical patient. Illustrations have been greatly expanded and technical surgical details have been included when deemed appropriate.

We are grateful to our many readers who have demonstrated their enthusiastic response to Volume I, many of whom also offered constructive criticisms, all of which have been incorporated in the present volume. We also wish to thank the contributing authors for their valuable time and efforts in helping us to achieve this goal.

Walter F. Ballinger, M.D.
Theodore Drapanas, M.D.

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THEODORE DRAPANAS

Practice of surgery: current review

Volume II

1

Emergency medical services

ALLEN P. KLIPPEL

Emergency medical services are those essential services that are urgently needed in order to provide medical care to the acutely ill and injured. The full and proper development and integration of each component service with the other emergency medical components yields a system for emergency medical care for that particular location. It is an unfortunate fact of modern American society that in few communities are such component services available, much less fully developed and coordinated into anything that even remotely could be called a system.

This lack of an adequate system for emergency medical care in most areas of the United States is the product of a number of factors. Physicians and hospital administrators are fearful of some of the constraints imposed by such a complete service. Most local governmental authorities, ever jealous of their own bailiwicks, are concerned about losing some of their autonomy and are also hesitant to suggest any programs that might increase the taxes of an electorate characterized as being in a taxpayer's revolt. The general public has never been made to understand what constitutes excellent emergency medical care and so has not been willing to spend the tax money to develop a system for their community. The end result is that the medical care available for most of the acutely ill and injured is so fragmented and uncoordinated that it can best be categorized as a "nonsystem."

An emergency medical services system implies that the emergency patient will readily enter into a sequential program that is designed to guarantee him or her an optimal chance not only to survive but also to be restored to a normal, productive life. It must be understood that the system only begins with the prehospital management of the patient. Every emergency medical service system worthy of the name must consider not only transportation into the emergency department of the hospital, but also whether in that institution there is available

prompt, proper care in the emergency department and appropriate transfer to whatever hospital inpatient facility is required next, be it a room, an operating suite, or an intensive care unit. Therefore an emergency medical care system may be divided into two sections—prehospital and in-hospital, including the emergency department.

Prehospital emergency medical transportation has been considered in depth in other texts[21] and will be reconsidered here only briefly. The other facets of prehospital care are the training of the crew and the communications network, without which no system can be developed.

TRANSPORTATION AND PERSONNEL

An ambulance, as defined in *Ambulance Design Criteria* published by the U. S. Department of Transportation,[1] is a vehicle that has at least 54 inches of inside headroom (preferably 60 inches), the width of the patient compartment being 72 inches and the length at least 116 inches. These dimensions allow the minimum space necessary for airway control, cardiac resuscitation, and intravenous fluid administration. It is obvious from these figures that the low, sleek, hearse-type ambulance should be replaced by a "resuscitation vehicle." These latter vehicles are frequently produced as a demountable ambulance body on a truck chassis or a van-type vehicle. Such ambulances have snobbishly been referred to as "bread trucks." Certainly the ride provided in this variety of vehicle is not as smooth as in a hearse type, but enough room is provided to allow a trained technician to work; obviously it is better to survive in a bread truck than to expire in a limosine. The resuscitation vehicles are also considerably less expensive, costing about $14,000 when fully equipped to comply with the standards suggested in the "Essential Equipment List" published by the American College of Surgeons.[4] The hearse-type vehicles, on the other hand, cost approximately $18,000 to $21,000 without even an oxygen tank.

The Med-Evac helicopter swooping down Valkyrie style to rescue the sick and injured has captured the public fancy and with certain valid reason. The evidence from Korea and Vietnam has documented that prompt evacuation to a proper medical facility can reduce the mortality of wounded combat troops.[26] The problem has been to translate this experience into the civilian setting where the costs of such programs must be balanced against the anticipated savings in life. The cost of operating a helicopter and crew is expensive.[13] But disregarding the costs the helicopter still has only a limited application in the management of real medical emergencies in the rural parts of the United States and even less in the metropolitan areas. What is forgotten in many of the discussions about helicopters is that the medical technicians who ride these military vehicles are highly trained and no doubt contribute heavily to the improved salvage rates. The combat aidman can start intravenous fluids, control hemorrhage, insert various tubes, and maintain cardiopulmonary functions before and during transportation to the hospital.

All of this is not to say that the helicopter is to be ignored in planning systems for emergency medical care. Rather it is essential that the public enthusiasm for the "whirlybird" be directed so that the funds made available for emergency care are employed to developed all facets of the system, not helicopters alone. It is also essential for the general population to be educated to understand that

if a helicopter is used, there must be sufficient room for trained technicians to minister to the patient. An airborne station wagon is little better than its ambulance counterpart on the highway and should be avoided for the same reasons of inadequacy.

One possible method to make available a properly large, properly staffed helicopter is to use the regular military vehicles and crews and allow the cost of operation to be assumed by the U. S. Department of Defense. This has been done in several areas with mutually beneficial results. The Army has used Med-Evac helicopters and crews in conjunction with state highway patrols and sheriff's departments in eight areas of the United States under the MAST program (Military Assistance to Safety and Traffic). MAST helicopters have assisted with on-the-scene care, but 70% of the time their real value is in transporting patients with sophisticated problems from rural facilities to larger, better equipped metropolitan hospitals. The military benefits by maintaining the skills of its personnel in real experience instead of in practice sessions.

However, testimony given at the hearings on emergency medical legislation indicated the cost of helicopter transportation in the MAST program to be in the range of $1000 per patient trip.* This is not a cheap ambulance service.

Ambulance personnel

Dunlop and Associates, Inc., of Connecticut[14] made a study, at the request of the U. S. Department of Transportation, on the economics of ambulance services. It was concluded that the major expense of an ambulance service was the personnel, with 60% to 70% of the cost of operating an ambulance company being the payroll.

From the Dunlop report it was determined that a private ambulance service, in order to be a profitable operation, must serve an area of no less than 60,000 people. (These figures are based on the assumption that 1 to 1.5 calls for an ambulance per day are generated by 10,000 people.) Therefore, using the minimum pay scale, at least six calls per day must be referred to one "for profit" ambulance company. However, it was also found that private companies collect less than 50% of their bills and frequently can only make a profit when their ambulance service also provides home-to-hospital transfers and sick room supplies, or when they are associated with the operation of a mortuary service.

One ambulance manned by two people working 40 hr per week requires that 10 people be hired if the service is to be provided 7 days a week, 365 days a year, and the personnel are given holidays and vacations. Outside of the large cities, in eastern parts of the United States volunteers man many of the ambulances. A volunteer ambulance service requires that about 30 people be available for each vehicle to be constantly in service. One full-time person is needed to make up the assignments, order supplies, and check on vehicle maintenance. The volunteer is well motivated, but because of the demand of his primary job does not usually have enough time to take really advanced training.

Funeral homes traditionally provided ambulance transportation as a public service and also with the expectation of performing the funeral should the victim

*Reported during hearings before the Subcommittee on Public Health and Environment, Committee on Interstate and Foreign Commerce, House of Representatives, 92nd Congress of the United States, second session, 1972.

die. This is not to imply that all mortuary-based ambulance companies are death oriented; some are excellent services. But in years gone by many mortician-operated ambulances were manned by untrained personnel, e.g., college students working for their room and board or other unskilled people who worked for relatively small wages. The federal laws for minimum wages, equipment, and training are now forcing the funeral home operators to meet proper standards or to leave the business, and it can be anticipated that most remaining morticians will abandon the ambulance business in the near future. It must be understood that any private or mortuary-based ambulance service that is now providing good emergency care and is willing to continue to meet the standards for training and equipment should be allowed to continue operation and in addition probably will need to be protected by a local subsidy and/or a franchise area to maintain financial stability.

The hospital-based ambulance can be the ideal ambulance service. By operating an ambulance as an extension of the hospital emergency room, it is assured that the hospital will be alerted to any medical problem that may be on the way to its doorstep. Moreover, the ambulance personnel, when they are not out on a call, could work in the intensive care and inhalation therapy units as well as in the emergency department of the hospital. The ambulance personnel would profit from such ongoing training, and the hospital would have part of the cost of the ambulance operation defrayed by using these people to help staff the other facilities.

An ambulance service could be developed in conjunction with the local fire service, but in this circumstance it should be under the guidance of a physician to ensure medical orientation. In addition to medical guidance, a sufficient number of men must be available. It is a common fallacy on the part of some city administrators to assume that the same number of men available for fire duty can take on the additional responsibility of ambulance service since they are not out working a fire all the time. Therefore the city fails to hire more firemen to man the ambulance, ignoring the fact that when there is a fire there can be no ambulance service or if the ambulance has been dispatched there are not enough men to man the fire equipment. The best ambulance services developed in fire departments have avoided this pitfall by hiring men to work on the ambulance as their only duty.

Another problem for some of the fire department ambulances has been the lack of promotion opportunities for the ambulance personnel. Most fire services require that a man go back into fire fighting in order to be promoted to a higher grade. However, the stable employment and pension plans available in most fire services have been major advantages to having the ambulance manned by firemen especially trained for ambulance duty.

Adequate training of the ambulance technician is mandatory. The *Advanced First Aid and Rescue Course* of the American Red Cross[6] requires about 50 hr of training, and the training program of the American Association of Orthopaedic Surgeons[2] requires about 35 hr; however, both of these programs are inadequate for primary training. The AAOS course is excellent as a refresher program, but the advanced Red Cross training program as presently designed is not adequate training for ambulance personnel. In both courses the material is usually presented in a concentrated fashion, crammed into only a few days' time.

The best minimum course is the basic training program for emergency medi-

cal technicians developed by the Department of Transportation. It is designed to be given as twenty-five 2 to 3 hr lectures and training sessions followed by 10 hr of in-hospital experience. These sessions are usually held once a week, and subsequent testing has revealed good retention of the presented material by the students in contradistinction to 3- to 4-day crash courses, the students of which demonstrated poor retention.

Students that have satisfactorily completed the 81 hr program are eligible to take the certifying examination of the National Registry of Emergency Medical Technicians. The certificate is now recognized in most states as indicating an emergency medical technician with documented training and demonstrated proficiency. More elaborate in-depth training programs are being developed and are underway in a number of communities either under the sponsorship of a hospital, e.g., the paramedic training program offered by the Los Angeles City and County Fire Department and Harbor General Hospital, Los Angeles, California, or a community college, e.g., the emergency medical technician program offered by the Junior College District of St. Louis and St. Louis County, St. Louis, Missouri. In these programs the student is taught to start intravenous fluids, administer certain drugs, and give countershock treatment to patients in ventricular fibrillation. They are also instructed in respiratory intubation as well as in the passage of nasogastric tubes. These programs require 200 to 600 hr of study and training with practical experience.

Realistic pay scales for all full-time trained ambulance technicians must be established to ensure their continuation in this vital health service. Such highly trained persons cannot be expected to work for minimum pay scales. The poor pay presently offered reflects the economic problems of running a private emergency ambulance service. The turnover of personnel in such services may exceed 50% per year as opposed to the fire department personnel turnover rate of only 4% or 5%.[12] It is extremely poor logic to expect to keep trained personnel who can be paid better in other areas, and it is equally foolish to be forced constantly to train new men.

Many states have as yet no legal definition of what constitutes an ambulance or what the training and duties of ambulance personnel should be. The state of California has led the way in adopting legislation that spells out the activities of the "paramedic."* Until June, 1973, the state of Missouri had no legal definition of what constituted an ambulance or what equipment this vehicle should carry. At the same time that training of the ambulance crew was not required, a hairdresser had to have 1500 hr of formal training to cut and color hair and wigs. Missouri was far from being peculiar in this deficiency. Fortunately the 77th General Assembly of Missouri passed a law licensing ambulances and technicians.† The new law also empowers the trained "paramedic" to start administration of fluids, defibrillate, and administer cardiotonic drugs.

COMMUNICATIONS

Communications are the backbone of any system of emergency medical care. Without an efficient communications network the other parts of the system,

*Chapter 2.5, Article 3, Division 2 of California Health and Safety Code, July 14, 1970.
†Senate Bill #57, 77th General Assembly, State of Missouri, July, 1973; Missouri Statutes 190.100 to 190.195.

no matter how fine, will be uncoordinated and unable to achieve their potential effectiveness. An emergency medical service communication cycle consists of a sequence of events initiated by and in response to an incident.[9]

1. Incident: the accident or medical problem that requires assistance.
2. Detection: the mechanism by which the incident is discovered.
3. Notification: the action or series of actions by which the proper authorities are informed of the incident.
4. Dispatch: the mechanism by which the proper authority orders emergency resources to the incident scene.
5. Closure: the process that brings emergency resources to the scene.
6. Action: the acts by the emergency resources that alleviate the trauma of the incident. In a medical problem this would include not only transportation of the victim but also the rescue on the scene and the initial care during transportation.
7. Return to station: the return of the emergency resources to the station. The equipment is cleaned and prepared to respond again.

For each of the events in the sequence there is a corresponding communication need.

Incident and detection. At the present time visual sighting of an emergency medical problem is needed to initiate the notification chain. However, airplanes operating in remote areas are required to carry radio equipment designed to automatically transmit a signal if the aircraft is downed.[31] A similar system for automobiles has been proposed, but its implementation at this time is not likely since such devices cost several hundred dollars, and the public would be reluctant to pay for them.

Notification. A telephone network along major highways, especially at interchanges, as well as in metropolitan areas that incorporates the "911" concept should be developed to speed the notification sequence.[27] The 911 concept was first proposed in this country in 1967. In January, 1968, the American Telephone and Telegraph Company (Bell System) endorsed the idea and announced they would keep the number 911 available as a nationwide emergency number. This emergency number has been placed in service in 308 communities, including New York City, but because of switching difficulties and political problems it has not as yet been universally accepted. The 911 concept suggests that all 911 signals originating in any one area be answered at a location from which all emergency resources such as the police, firemen, and ambulances would be dispatched. In this 911 area even the pay phones should accept 911 calls without a coin. In the smaller communities where the sheriff's office or a similar agency handles all emergency calls, the system is easily developed. In large communities where the telephone system may cross political boundaries, problems of jurisdiction develop. In many metropolitan areas the police and fire departments do not have a single dispatching center. In other locations the fire department may be in a fire district with boundaries that correspond neither to a police district nor even to a single political unit such as a city.

In a metropolitan area a single dispatch center could be troublesome because adjacent cities may have streets with the same or similar names. Therefore it would be necessary for the caller to identify the origin of the call and consequently to indicate which emergency unit should respond. To answer some of

these problems a computer-programmed system called "Automated 911" has been designed. The introduction of the automated system allows for a number of separate dispatching centers. When 911 is dialed, that call is automatically switched to the dispatching center for that subarea. It is obviously necessary that in each subcommunity the police, fire, and ambulance service areas be made the same.

There still remains the objection that the dispatching is not done by the personnel of the particular police or fire department. These services complain that only someone from their department can get the proper information to guide the dispatching of the proper vehicles. Also, because of political problems, some fire and police officials are reluctant to realign their districts. These latter objections are not valid, assuming the dispatchers have been properly trained; the jealousy over political fiefdoms should be made subservient to the needs of the public.

The cost of even the nonautomated 911 system could vary considerably and could be expensive to install, depending on the need for switching equipment and dedicated ground telephone lines. Any cost, however, would be relatively small to each subscriber and little price to pay to be assured of prompt help in time of need. Since about 20% of the citizens of the United States move annually, and since most people do not bother to learn their new local emergency numbers until faced with the need, to have a nationwide emergency number such as 911 would improve the public's ability to summon help.

Even without the 911 system, if standard telephones were available along the major highways at interchanges and at high-accident sites, considerable improvement in the early notification that an emergency situation exists would result.

Dispatch. Dispatching the necessary emergency equipment can be done in one of three ways or in a combination of these. A telephone call from the dispatch center to the indicated station can be initiated over conventional lines or by using a dedicated (hot) line, bypassing the usual telephone switching system. Since the lines of the telephone networks are installed above the ground, they are subject to damage in natural disasters. The overloading of the system that occurs in disasters can cause the telephone network to shut down in order to protect itself. As a result, if dispatching is done by a telephone system, a back-up system of radio dispatching is necessary. Obviously the radio must be used for dispatching if the emergency vehicle is cruising and away from a telephone.

In metropolitan cities with a heavy load of dispatching calls, a single radio frequency may be assigned to each police or fire subdistrict. In this event each vehicle must have at least two radio frequencies—its own district channel as well as a command channel that is used to talk to all the area vehicles at one time.

Teletype communications are also being developed. The dispatcher gives the emergency personnel their destination vocally and simultaneously supplies them with a written message. The newer teletype machines are radio operated and can be installed on each vehicle so that the message can be transmitted even when the vehicle is away from the station. These teletype dispatching machines also include a memory coil. This enables the operator to collect information from the caller, and only when he is sure which unit should be dispatched does he transmit the message by pushing the transmitter button.[35]

Closure. During the time the emergency unit is in transit to the scene the personnel may be given additional information by radio from their dispatcher to guide them. When the unit has arrived, the radio may be used to request additional help from other sources such as the police, the fire department, additional ambulances, or wreckers.

Action. The need for radio communications during on-the-scene management is obvious. The emergency medical crew should be in communication with a physician to advise them as to the care of the patient and to authorize advanced treatment. The patient's physiologic data such as the ECG may be transmitted. On the way to the hospital the radio would again be used to notify the hospital concerning the condition of the patient they are about to receive.

Return to station. While returning to base the crew would notify the dispatcher that they are ready for another assignment.

Terminology. To understand the allocation of radio frequencies for emergency medical care it is necessary to present certain abbreviations, definitions, and technical data.[15]

Hertz (Hz)	Cycles per second
Kilo (k)	1,000
Mega (M)	1,000,000
Giga (G)	1,000,000,000
Tera (T)	1,000,000,000,000

Radio spectrum frequency bands

Very low frequency (VLF)	3-30 KHz
Low frequency (LF)	30-300 KHz
Medium frequency (MF)	300-3000 KHz
High frequency (HF)	3-300 MHz
Very high frequency (VHF)	30-300 MHz
Low band	30-50 MHz
High band	150-175 MHz
Ultra high frequency (UHF)	300-3000 MHz
Super high frequency (SHF)	3-30 GHz
Extremely high frequency (EHF)	300-3000 GHz (3 THz)

The frequencies used for mobile land radio communications are most commonly in the low band or high band ranges of the very high frequency (VHF). The low band frequencies have a long-range capability but also may skip for great distances, which is undesirable. However, the American Red Cross has kept its radio transmissions on low band (47.42 MHz) throughout the United States.

The high band frequencies (150 to 175 MHz) have been allocated for general emergency and medical radio communications and are the frequencies most used for interhospital calls, ambulance dispatching, and police work. The transmission distance is less with the high frequency band but little skip occurs.

The ultra high frequency (UHF) bands have a shorter range than the VHF channels, but there is no skip and almost no noise interference. UHF frequencies penetrate buildings well, which is obviously desirable in a metropolitan area; however, the UHF waves tend to be absorbed by foliage.

The following data illustrate the differences in low band, high band, and UHF performance. Using a power output of 100 watts and an antenna 100 feet in height, the transmission ranges can be compared as follows:

Low band	28 miles
High band	21 miles
UHF	17 miles

Transmission and receiving are both on the same frequency in low band and high band communications; i.e., when one station, either the base or the mobile, is transmitting, the other unit can only receive. This is called the "simplex system" and is necessary because noise interference makes impossible the simultaneous use of close frequencies in the VHF range. Because noise interference is absent in UHF transmissions, the use of paired adjacent frequencies, termed the "duplex system," is possible, so that a station can both send and receive at the same time, and conversations with other units are similar to those possible over the telephone.

• • •

Communications in an emergency medical services system may be summarized as necessitating the following components:

1. The ability to make emergency calls from all telephones in the area by dialing 911 (These calls would be received in one dispatching center [emergency operating center] that is capable of managing all emergencies for that specific area or subarea.)
2. Available telephones, especially with the 911 or a common emergency number, at sites along expressways and at major intersections
3. Dispatching centers with not only telephones but also radio (or teletype) communications with all emergency services
4. Each ambulance able to communicate with:
   a. Dispatcher
   b. Hospitals
   c. Other emergency services (via the dispatcher)
5. Transmission of physiologic data available
6. Hospitals able to communicate by radio with each other in their area

In the United States an interhospital communications network is being developed on frequencies especially assigned for this use by the Federal Communications Commission (FCC). All the hospitals in one region can communicate by radio with each other on 155.340 MHz. In addition, a few hospitals, called "regional hospitals," have another frequency (155.280 MHz) that is to be used to communicate with hospitals in adjoining regions. By this method a message can be passed from one regional hospital to the next, and in essence a communications network across an area or state can be developed without land lines.

With the installation of radios for interhospital communications, an opportunity presented itself to many hospitals to develop intrahospital paging for key employees and officials. This use has so loaded the frequencies as to cause interference with the emergency medical uses. To make intrahospital paging possible, the FCC is considering allocating 157.450 MHz or other VHF channels now reserved for business use. The commission is also considering channels in the low band range (30 to 50 MHz).[17]

Since the ambulances and hospitals both had VHF radios, some programs of ambulance-to-hospital transmission of ECG's were begun. This also interfered with the hospital networks. On March 23, 1972, the FCC provided eight base-

mobile frequency pairs in the 460 MHz bands for transmission of biomedical data. At the same time it prohibited further use of the VHF channels for such telemetry. Two frequencies in the UHF range were retained to be assigned only for central ambulance dispatching in coordinated, areawide communications plans using telemetry.

A communications authority must be developed not only in local areas but also statewide to coordinate and supervise the use of emergency medical radio frequencies. This authority will have to cooperate in its activities with those in adjacent states, since radio waves do not respect city, county, or state lines. As a result, unless there is regional development of the emergency communications system, one ambulance dispatcher may find himself in competition with a police dispatcher in the next state, and the interhospital network could be preempted by in-hospital paging or ambulance dispatching.

In developing a statewide system for emergency medical communications, planning for a microwave network should be considered. In the microwave system, a VHF receiver picks up a VHF transmission at the tower. In the receiver the signal is automatically converted to the giga hertz range and carried over wires to an adjacent tower to be transmitted to the next tower, where the receiving antenna is a 6-foot "dish." Each dish must be in the line of sight of the transmitting and receiving equipment; depending on the terrain, the towers are placed about 25 miles apart. Approximately 300 channels are available from a 2 GHz transmitter. The transmission of a television picture and voice requires approximately 270 of the channels, reducing the channels available for other uses. However, several dish antennas can be installed on each tower and connected by wire to adjacent transmitters.

The television transmitter and receiver cost approximately $5000 per tower, and each voice channel costs approximately $1600 for each tower. A rough calculation is that the minimum cost of a microwave system averages about $2000 per mile covered. Maintenance costs approximately $60 per tower per month.[31] The system is not cheap, and yet if properly designed to include radio transmissions for a number of state agencies such as the Conservation Commission, Highway Department, and Highway Patrol, the cost approaches that of conventional land lines and telephones.

Using a microwave system, television images could be passed from a rural hospital to a medical center along with voice communications to help in the management of a patient with an unusual problem. The value of the system in connecting computers, in providing statewide education programs, or in transmitting data and voice messages as well as television between states is obvious. The idea of an intra- and interstate microwave system is in its infancy, but can be expected to develop rapidly.

The use of laser beams for long-distance transmission of radio frequencies is now under study, but as yet cannot be considered as practical.

HOSPITAL PHASE

That the hospital is the destination for most acutely ill and injured patients is obvious, but which hospital? In a community with only one hospital there is no problem because there is no choice. The local physicians and ambulance personnel know that any patient must be delivered to the one hospital, and if

there are deficiencies in that institution, it is incumbent on these men to work to improve the situation. It is also the obligation of the medical and hospital administrative personnel of these less well-equipped institutions to develop systems for the transfer of patients requiring more sophisticated care. Without these arrangements considerable delays can and do occur, and the patient's condition may deteriorate as a result.

A problem arises in the area with two or more hospitals. There it is necessary to decide if one hospital is better equipped and staffed to provide the care for certain patients and then to inform ambulance crews and other emergency personnel as to where to take those few critical patients. In 1968, consideration was given to categorizing hospital emergency department facilities.[7] The backup services and staffing available in the hospital itself were only superficially considered, but the system of categorization listed the best facility as a number four and the least qualified as a number one. When the AMA and others developed their system of categorization of hospital emergency capabilities, the best qualified institution was classed as number one and the least qualified as number four.* This results in confusion.

Those who have watched football games have grown accustomed to seeing fans running around holding one finger in the air and shouting, "We're number one." This same chauvinistic attitude has been carried into the hospital administrative field with unfortunate results. The fear has been expressed by hospital personnel that the public will not understand that the emergency capability of an institution does not indicate its ability to provide other types of medical care. The hospital administrator, usually at the urging of his board of trustees, may try to secure categorization as a number one institution, which is basically a university research hospital, but it may be unable to meet the standards of the AMA or other organizations. As a result, local categorization may be done, ignoring the top AMA categories and starting with the general emergency service system as a number one institution. This system may preserve institutional pride, but it does not help emergency personnel decide where certain catastrophically ill or injured patients should be taken.

AMA category I—comprehensive emergency service†

Scope of capabilities

The hospital shall be fully equipped, prepared, and staffed to provide prompt, complete and advanced medical care for all emergencies including those requiring the most complex and specialized services for adults, infants and children, including newborns. It shall have a capacity adequate to accommodate the direct and referral patient loads of the region served and be capable of providing consultative support to professional personnel of other hospitals and health facilities in the same region.

It is required that the emergency department be staffed at all times by experienced physicians and nurses and that all necessary equipment for resuscitation and control of any patient be available. It is also required that there be

*Categorization of hospital emergency capabilities, recommendation of the conference on guidelines, Chicago, 1971, American Medical Association Commission on Emergency Medical Services.

†Experienced physician when applied to residents in training in that hospital means those with more than two years of residency training; when applied to other physicians means one with more than two years' experience following graduation.

at all times in-house staffing by experienced physicians, including an operating team headed by an experienced surgeon. Laboratory facilities including a blood bank must be available and staffed as must a radiology department be manned at all times. A radiologist must be in-house.

The hospital must have available appropriate intensive care areas, including facilities for children and newborns. The hospital is to have a helipad available as well as equipment to communicate with helicopters and ambulances.

AMA category II—major emergency service

Scope of capabilities

The hospital shall be equipped, prepared and staffed in all medical and surgical specialties to render resuscitation and life support for adults, children and infants including newborns. It shall also supply definitive care for all such patients except the occasional patient who requires follow up care in very specialized units. Transfer may be necessary and shall be under prior agreement with other hospitals.

In this type of institution the emergency department must be staffed at all times by an experienced physician and nurses. Equipment must be available to cope with all emergencies. The hospital must have in-house physicians and other personnel, including an in-house anesthetist or anesthesiologist, to staff the operating suite as well as to provide complete emergency medical care.

Blood bank, laboratory, and radiology facilities are to be available and staffed by technicians. Intensive care areas are to be available. Communications are to be established between hospitals as well as with the local ambulances.

AMA category III—general emergency service

Scope of capabilities

The hospital shall be equipped, prepared and staffed in the medical and surgical specialties necessary to render resuscitative and life support care of persons critically ill or injured of all ages. The availability of supplementary specialty service shall be prearranged with nonstaff specialists. Transfer of patients for specialty care shall be by prior agreement with other hospitals.

The emergency department and the hospital shall have an "on call" physician available in-house. The emergency department personnel shall be trained in emergency procedures, and equipment shall be available for these procedures.

The ancillary services of the hospital such as the operating room, laboratory, and radiology department can be staffed by people out of the hospital but readily available. An intensive care area for medical and surgical patients will be available with monitoring equipment. Communications for in-hospital service will be available as well as two-way radio communications between hospitals, ambulances, and appropriate emergency personnel.

AMA category IV—basic emergency service

Scope of capabilities

The hospital shall be equipped, prepared, and adequately staffed to render emergency resuscitation and life support medical services for patients of all ages. Transfer, where necessary, shall be under prior agreement with other hospitals.

The emergency department will be staffed by an experienced nurse or licensed practical nurse who has had training in emergency procedures. A physician will be on call for the emergency department from outside or elsewhere in the hospital.

The ancillary laboratory, radiology department, and operating room personnel can be on call from outside the hospital. Communications between ambulances and other hospitals shall be available.

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If every hospital in a metropolitan area were to keep a full operating team, a radiologist, an anesthesiologist, and laboratory and radiology technicians in-house 24 hr a day and 7 days a week, the cost in that hospital for each emergency case would be prohibitively high. From the standpoint of economy, it makes good sense to collect extreme emergency cases into only a few hospitals; these institutions can justify the cost of complete care being available around the clock because the personnel would be fully used.

However, in many communities hospital categorization is as yet an unresolved problem. In some areas the hospital association has done the survey, and in other communities that task has been performed by the comprehensive health agency or local medical groups. In many locations nothing has been done because of doubts and fears. What is missed by physicians and hospital administrators is the understanding that the categorization criteria promulgated by the AMA are only guidelines and are not to be rigidly interpreted. Moreover, almost any hospital large or small, university or community fulfills the guidelines for at least category II at 10 o'clock on a weekday morning. At that hour of the day the laboratory, radiology, and operating facilities are fully and completely manned. Most hospitals at that time could provide the care needed by almost any emergency patient. The problem is during the night and over weekends. What may be necessary is nonrigid or updated criteria, i.e., "status categorization." Depending on the changes in staffing, a hospital could be in category II or even I up to the late afternoon and then assume a lesser designation.

Also, it must be considered that possibly a patient should not be taken to the category I or II hospital if these institutions already have their operating suites, etc. fully loaded. Even a large university medical center can be swamped by five or six patients from a multiple car crash all requiring some sort of surgery. In this instance it might be quicker for the category III hospital to collect its personnel and physicians and to open the laboratory and operating areas than to wait for the facilities to become available in the category I institution.

Moreover, too much consideration has been given to the acutely injured patient, forgetting that patients with heart attacks and medical problems constitute a population much greater than trauma victims. Almost every hospital in the metropolitan areas as well as most of those in the rural communities have intensive care areas with electronic monitoring.

No coronary intensive care area is better than the personnel staffing the facility. In many of the smaller hospitals, the nurse in the coronary care unit may be better qualified by excellent training and long experience than an intern or first-year resident to supervise the care of the patient with a fresh myocardial infarction. Thus a hospital that is a category III for a trauma patient may be a category I for a patient with a heart attack.

This concept is equally applicable to other areas of medicine. A hospital by virtue of a special interest on the part of its medical staff may develop a sophisticated medical area such as a respiratory intensive care area or a kidney unit. For

the patient with an acute respiratory or kidney problem, this hospital may be the best source for immediate care in that community.

To make the concept of "status categorization" applicable, one local office must be established to keep a running account of the available beds in various intensive care areas as well as the status of the prime receiving institutions. This office could be the headquarters of the hospital association or a community emergency operating center. The information would be imparted to the ambulance dispatcher at regular intervals during both the day and the night.

EMERGENCY DEPARTMENT STAFFING

The public demand that expert medical care be available at all hours of the day or night has resulted in an ever-increasing load on the emergency and outpatient areas of almost every hospital in the United States. Figures from prepaid medical groups indicate that each month between 0.04% and 0.1% of their patients present themselves in an emergency facility.[28] Also, assuming a stable population from which a hospital draws its patients, the use of the emergency department can be expected to increase by almost 10% per year.[29] No good explanation of this is available, and the best guess is that the public now expects to see a physician for complaints that in days gone by would have been treated with home remedies or by the local pharmacist with patent medicines.

This increasing patient demand has produced a significant change in the physician staffing of the emergency department. Gone is the day when the intern, busy elsewhere in the hospital, would be called to see a patient in the emergency room. This "emergency room" was usually a small, poorly equipped area where the intern or attending physician would see patients to suture minor lacerations or to order x-ray films. Most of the actual treatment was done in other areas of the hospital. Certainly the staffing and facilities were of a low level.

Now the emergency department may be the area in a hospital where the most sophisticated medical care is provided. It has become apparent that a junior intern is not the person who should be supervising this type of care. As noted before, the guidelines of the AMA reflected this change by defining an emergency department physician as being experienced only when he is in his third postdoctoral year of training or practice. It is also apparent that not every physician is equally qualified to practice all types of medicine in every hospital. A landmark lawsuit in 1965* firmly establishes that it is the duty of the hospital to supervise the care that every patient receives in that institution and that if incompetent care is provided for a patient, the hospital as well as the physician is liable for financial redress. At a recent medicolegal symposium sponsored by the AMA and the American Bar Association, Morris suggested that the following precautions be followed to avoid lawsuits[25]:

1. Every patient must be seen by a fully experienced physician and not left to the judgment of interns, residents, or nurses.
2. Every patient should be admitted unless or until a qualified doctor rules out the necessity for hospitalization.
3. The hospital should not employ any foreign physicians who do not speak

*Darling vs Charleston Community Hospital, 33 Ill. 2nd 326, 211 N.E. 2nd, 14 ALR 3rd 860, certiarari denied 86 Supreme Court 1204, 383, U. S. 946, 16 L. Ed. 2nd 209.

fluent English, or if it must employ them they should not be allowed to take histories or give instructions or orders. Any patient assigned to them should be closely monitored.

4. The patient who receives temporary, old style emergency care or his representative should be given a written statement that he must see another doctor within 24 hours. A copy of this statement should be filed with his record.
5. Patients with the following conditions should not be discharged from the emergency department without the approval of a qualified physician, preferably the appropriate specialist: possible head injuries, lacerations that may involve tendons or nerves, obscure but worsening symptoms, and chest pains or shortness of breath.
6. Containers of vomitus should be saved in suspected poison cases, and the proper antidote should be checked before administration if there is any doubt.
7. No drugs should be administered without recording a negative history of allergy or without proper tests, and then only by a licensed physician.
8. Accurate records should be kept of all visits, including those in which the patient is not examined and treated but only given advice or referred elsewhere.
9. A radiologist should scrutinize every x-ray film, border to border, including the portion covered by clips. Extreme care must be used when x-raying the gonads of patients, especially women within the childbearing years.

To answer the demand for more highly skilled emergency department physicians a number of plans have evolved. In 1961 at Pontiac Hospital, Pontiac, Michigan, a contractual arrangement for staffing the emergency department was initiated.[23] The plan is based on a contract between a corporation representing a number of physicians and the hospital; in this contract the corporation guarantees that physicians will be in the emergency department at all times. The corporation represents a rather large number of physicians who remain in private practice but who agree to spend a part of their working hours in the emergency department of the contracting hospital. The corporation is governed by an executive committee or board of directors and an overall director who schedules the staffing times, determines payments to the physicians, and negotiates the arrangements with the hospital.

Each physician is liable only for his own acts. The corporation has the legal benefits of limited liability, continuity of life, and centralized management. It also has a great advantage in income tax savings, for the professional medical corporation may withhold income from taxes for the following:

1. Pension plans
2. Profit-sharing plans
3. Health, accident, and life insurance
4. Deferred compensation

The participating physician is able to continue in private practice, since he can spend as much or as little of his time as he wishes in the emergency department, but this has been considered a disadvantage of the program. It is feared by other physicians, who are not involved in the emergency department corporation, that the emergency department physician may take his hospital patients

into his private practice. Another disadvantage is that even with a large group of physicians it may be difficult to schedule the shifts that each physician wants and at the same time to provide the coverage for the emergency department that the hospital must have.

Also in 1961 in Alexandria, Virginia, four physicians who had been in the private practice of family medicine gave up their practices and started full-time coverage of the Alexandria Hospital Emergency Department.[24] These men had been part of a committee that was given the responsibility of providing coverage for the emergency department. Using foreign graduates had been less than satisfactory, and the emergency department nurses had been required to call a physician in from outside the hospital each time a patient came in. This group made the assumption that emergency department service was a full-time function and could not be associated with any private practice by the staffing group either outside the emergency department or involving in-hospital patients. The Alexandria physicians were careful to refer any patient back to his original physician and to choose the consultants with respect to the needs of the patient and the wishes of the private physician and the aid of the chief of service involved. The chiefs of service were required to provide a monthly roster of specialists in each area. This resulted in excellent acceptance of the emergency department group practice concept by the hospital staff physicians.

In both the Alexandria and the Pontiac plans the corporation (in the name of the emergency department physician) submits a bill for the services that is separate from the hospital charge. The charge within each program is uniform for the same service irrespective of which physician administers the care.

In Alexandria the hospital accounting and billing departments handle the doctors' bookkeeping and billing and charge the corporation 15% of the fees collected for the service. The Pontiac corporation has billed the patient completely separately from the hospital accounting service in order to avoid any conflict with the Internal Revenue Service.

Coverage of an emergency department by full-time physicians requires that four doctors be employed, assuming an annual patient load of at least 18,000. It has been calculated that when the number of visits approaches 30,000, a fifth physician is needed to help cover the evening shift and to assist during weekends. An emergency department that sees fewer patients will have to consider only the Pontiac plan, which can be used when the visits are as few as 7000, since a physician need be present only when a patient arrives and can be elsewhere in the hospital the rest of the time.

In university hospitals the house staff may still provide coverage for the emergency department as a part of their learning experience. This method is satisfactory as long as experienced residents supervise the interns in effect as well as on paper. A full-time physician may be responsible for operation of the emergency department, but his role is the supervision and teaching of the house staff and not patient care.[3]

In 1971 a new type of staffing for the emergency department was proposed by Wyker et al.[34] from Holyoke Hospital, Holyoke, Massachusetts. It was considered that while the Pontiac plan ensured that there would be a physician in the emergency department at all times, and the Alexandria plan provided a physician dedicated to emergency medicine, both types of physicians were con-

cerned only with the medical care delivered between the entrance and the exit to the emergency department. The Holyoke plan is to develop a physician dedicated to crisis care medicine who would be concerned with the illness or injury beginning with the initial contact through the emergency department and into the intensive care areas.

Safar and Granvik[30] in 1971 proposed a new facet of medical practice to be known as "critical care medicine." Critical care medicine is composed of the triad of resuscitation, emergency medicine, and intensive care medicine. Safar defined the critical care medicine physician as an "intensivist." A scientifically trained, highly motivated clinician, the intensivist should have the action-oriented attitude of the anesthesiologist and surgeon, the thoughtfulness of the internist and pediatrician, the inquisitive, data-oriented mind of the scientist, and the diplomacy of a United Nations ambassador. The role of this intensivist would be as team leader, coordinating the other disciplines involved with the care of patients in the intensive care unit.

Wyker[34] proposed that a subdivision of critical care medicine was primary crisis medicine (PCM), whose practitioners are to be responsible for developing disaster medicine programs, including advanced cardiopulmonary resuscitation. As designed PCM would also be deeply involved with the advanced training of those persons who are most likely to be first on the scene of a medical disaster, i.e., the police, firemen, or ambulance personnel. In addition, the PCM physician would be involved with the supervision and development of telemetry systems and with the training of technicians. His primary functions would still be in the emergency department, but he would extend the assets of that department to the scene and be responsible for the patient from the scene until the patient is delivered to the next eschelon of component care.

As the public is increasing its demand for emergency and outpatient medical care from the emergency department of hospitals across the United States, more physicians have decided that this is a developing aspect of medicine, and, following the Alexandria and Pontiac plans, increasing numbers have made this a new or second career. In October, 1969, in Lansing, Michigan, a group of physicians interested in emergency medicine met and formed the American College of Emergency Physicians (ACEP). The aims of the organization as stated were the following:

1. To establish standards of emergency medicine
2. To encourage and implement the training and continuing education of emergency physicians
3. To study and analyze the socioeconomic aspect of the practice of emergency medicine
4. To promote the education of the general public and of patients who may require emergency care
5. To promote research that will result in improving the practice of emergency care
6. To promote the coordination of community emergency care facilities and personnel
7. To promote any policy that preserves the integrity of private practice
8. To provide official political and social representation for the emergency departments in organized and academic medicine

ACEP has grown rapidly and now has about 4000 active members. To answer the demand for the training of second-career physicians, a number of 2-week intensive training programs have been developed in emergency medicine. In these programs the already experienced physician is apprised of newer skills and is retrained in emergency medicine.

It also became apparent that the training of recent graduates of medical schools was needed, and residencies in emergency medicine were begun. The first resident in emergency medicine began his training July 1, 1970, at the University of Cincinnati Medical Center, Cincinnati, Ohio. The training was accredited for 2 years by the AMA as a family practice residency.

More of these programs have developed; 13 programs are under way in universities that are usually associated with large municipal hospitals; this ensures that the residents will treat a sufficient patient load to acquire adequate training. These 13 programs involve the following institutions:

University of Cincinnati, Cincinnati General Hospital, Cincinnati, Ohio
University of Southern California, Los Angeles County Hospital, Los Angeles, Calif.
Bowman Gray, Bowman Gray School of Medicine Hospital, Winston-Salem, N. C.
University of Missouri–Kansas City, Kansas City General Hospital, Kansas City, Mo.
University of Louisville, Louisville General Hospital, Louisville, Ky.
Michigan State University, St. Lawrence Hospital, Lansing, Mich.
Medical College of Pennsylvania, Philadelphia, Pa.
Wayne State University, Detroit General Hospital, Detroit, Mich.
University of Kentucky, University of Kentucky Medical Center, Lexington, Ky.
Tulane University and Louisiana State University, Charity Hospital, New Orleans, La.
Northwestern University, Evanston Hospital, Evanston, Ill.
University of Chicago, Billings Hospital, Chicago, Ill.
Washington University, St. Louis City Hospital, St. Louis, Mo.

In most of the programs now under way the majority of the time is spent in the emergency department of the primary institution. Outside rotations are suggested only in anesthesia, hand and maxillofacial surgery, and the intensive care areas of lung, heart, and surgical services.

ACEP, through its committee on graduate education, has provided the following guidelines for residency training in emergency medicine*:

I. The provisions of the General Requirements (Section 1-10) as stated in the "Essentials of Approved Residencies" must be met.
II. Special requirements for residency training in emergency medicine.
   A. Residency training in emergency medicine shall be designed to meet the needs of graduates intending to become emergency physicians. An emergency physician is a specialist in the immediate recognition and evaluation of and response to acute illness and injury; and in the administration, teaching, and research of all aspects of immediate (initial) care and disposition of any patient. The physician:

*Adapted from Guidelines for residency training in emergency medicine, Lansing, Mich., Graduate Education Committee, American College of Emergency Physicians.

1. Provides initial emergency health services to patients of all ages.
2. Evaluates patient's emergency health needs, providing such services as are immediately indicated, and if necessary refers patients to other appropriate physicians for further definitive care.
3. Ensures the availability of follow-up care, in or out of the hospital, as may be required.

B. Training period.
1. The duration of training shall be no less than 24, nor greater than 48 months following graduation from an accredited medical school.
2. Residents completing less than 36 months, but more than 24 months of training may become eligible for certification on receipt of a letter from their program director attesting of their competency.

C. Principles.
1. The program must be designed in such a manner that the resident maintains his identity as an emergency physician.
2. Ultimate integration and application of the skills, techniques, and procedures of traditional specialties in the provision of emergency care will be best learned in the emergency department when taught by emergency physicians.
3. The hospital and the emergency department are responsible for the administration of the residency program and should meet the following minimal requirements:
   a. There must be a full-time director of the emergency department.
   b. The emergency department should be constituted as a full and equal department within the hospital organization, with its own budget. The emergency residents should have similar stipends and from similar sources as those for residents in other specialties.
   c. The emergency department director must assume responsibility for the entire training program.
4. Training need not take place in one geographic location nor in one hospital, provided the training is coordinated to ensure completeness, and that the department director retains administrative control; and that the resident spends the majority of the time in the parent institution.
5. Each department shall hold regular meetings of the attending staff and residents for the purpose of conducting a program critique and evaluation. There shall be at least three such meetings per year.
6. Periodic in-training examination of the resident is required at least annually. Copies of the examinations and results shall be distributed to (a) the resident, (b) the program director, and (c) the Graduate Education Committee of the ACEP.
7. While in the emergency department, residents with less than 24 months' training must be supervised by senior emergency medicine residents and/or attending physicians who are on-site. Ideally, supervision should be provided by emergency physicians.

The AMA rejected the application to qualify emergency medicine as a separate specialty until July, 1973. At that meeting it was concluded that emergency medicine was a developing specialty of medicine and that consideration would be given to establishing the methods for certification as well as methods of identifying training programs.[5]

In 1969 at Birmingham, Alabama, physicians holding an appointment in a university and involved with the teaching in or the supervision of an emergency department met and decided that an organization dedicated to the planning and delivery of emergency medical services in the university setting was needed. They founded the University Association for Emergency Medical Services (UA/EMS). At that meeting, 138 physicians represented 96 of the existing 119 medical schools. The objectives of the association are as follows*:

*University Association for Emergency Medical Services Constitution Article II, Nov., 1970.

1. Collecting and disseminating information concerning the operation of emergency medical services
2. Providing a forum for the discussion of problems in emergency medical care and their proposed solutions
3. Aiding the university physician in the planning, administration, and provision of emergency medical services
4. Fostering education and research in the field of emergency medicine
5. Encouraging the university physician to take an active role at the local, state, and national levels in planning regional emergency medical services
6. Recommending guidelines for location, size, functional design, interhospital relationships, staffing of educational programs, and performance of hospital emergency services
7. Providing assistance in the evaluation and planning of emergency medical services on request
8. Recommending appropriate changes in national, regional, state, and local policies influencing or regulating emergency medical services
9. Encouraging recognition of the academic value of service in this field

Guidelines for establishing emergency department facilities

The UA/EMS is developing preliminary guidelines for the organization of an emergency department. Included in these unofficial recommendations are the following suggestions to calculate staffing needs in terms of space requirements (in square feet) of an emergency department facility*:

Patient care

Control and records†	150
Holding area	250
Waiting room (children and adults)†	1000
Extra waiting room†	140
Crisis (life threatening) treatment area	350-375
Major emergency treatment area (including area for supply cart and writing desk)	150
Major emergency treatment area (two patients)	250
Minor emergency treatment area	150
Nonurgent treatment area (one patient)	150
Specialty room (ear, nose, and throat, etc.)	150
Minor surgery operating room (not for general anesthesia)	150-175
Storage and cleaning facilities	200
Observation areas (provides 5 feet of free space around each bed)	
6-bed area	1200
12-bed area	2400
X-ray examination area (general, skull, developing, and viewing)	800
Hallways suitable for beds	8 feet wide

Education‡

Resources room (library, demonstration models, classroom, one-way viewing)	

*Adapted from guidelines for organization of an emergency department in the university setting, Augusta, Ga., 1974, report of the Committee on Emergency Department Organization, University Association for Emergency Medical Services.

†Based on patient load of 100 per day.

‡Based on 100 patients, interns, residents, and nursing staff to be educated per year.

Package (if in emergency department area)	500
Separate (if in another part of hospital)	800

Research

On-site	500
Laboratory space for analysis	500

Administration

Emergency department director's office	200
Nursing director's office	200
Secretary's area	200
Staff change room and lounge	400
On-call rooms (each)	200
Ambulance attendants' area	200

Mechanism for determining adequacy of a specific facility within emergency department

1. Surgery emergency department visits for a typical 2-week period. Identify patients by:
   a. Priority

      LT Life threatening
      U Urgent (major)
      NU Nonurgent (minor)

   b. Classification—surgical, medical, pediatrics, psychosocial, obstetrics-gynecology, other
   c. Census

      MDC Maximum daily census for 2-week survey period
      ADC Average daily census
      P Daily census during peak month
      X Daily census during month survey takes place
      MHS Shift survey period that has the peak census

   d. Average length of stay in facility

      ALS in hours
      $\overline{X}$ Ideal
      $\overline{C}$ Calculated from survey

2. Determine
   a. Census by month
   b. Yearly census
      (for year during which survey took place)
3. Calculations
   a. Maximum daily load:

$$\text{MHS} = \text{MDC(X)} \cdot \frac{\text{ADC(P)}}{\overline{\text{ADC(X)}}}$$

   b. Theoretic maximum heaviest shift:

$$\text{TMHS} = \text{MDL} \cdot \frac{\text{MHS(X)}}{\text{MDC(X)}}$$

   c. Maximum number of patient spaces needed per shift in each facility:

$$\text{MPS(C)} = \text{MHS} \times \%\text{NU} \times \text{ALS(C)} + \text{MHS} \times \%\text{U} \times \text{ALS(C)} + \text{MHS} \times \%\text{LT} \times \text{ALS(C)}$$

   d. Maximum number of patient spaces needed per shift if patient stayed in facility for ideal time limit:

$$\text{MPS(I)} = \text{MHS} \times \%\text{NU} \times \text{ALS(I)} + \text{MHS} \times \%\text{U} \times \text{ALS(L)} + \text{MHS} \times \%\text{LT} \times \text{ALS(I)}$$

4. Uses
   a. If MPS(C) = MPS(I), then the emergency department has the ideal number of facilities to take care of a maximum patient load on any shift.
   b. If MPS(C) > MPS(I), then the emergency department does not have the ideal number of facilities to take care of a maximum patient load on any shift.
   CURE: If average length of stay for U and NU patients is greater than ½ hr or greater than 1 hr for LT patients, decrease time spent in facility. If ALS is within optimal limits, build new facilities.
   c. If MPS(C) < MPS(I), then the emergency department is overstaffed for that particular facility.

It may be safely stated that few emergency departments in this country are adequate either in square footage or staffing. It is calculated that 3 to 4 years pass between the time it is decided to build a hospital with a new emergency department or to enlarge the existing facilities and their completion; in the meantime, the patient load continues to increase. It has also been suggested that if the new emergency department is efficient and well designed, the public will increase the utilization of the facility.[8] The rule of thumb is to double the population size now served to calculate the patient load in the new emergency department and to increase the square footage of the new facility to meet that demand. Since personnel is the most expensive item in any area of the hospital, a large, well-designed emergency department that is "open" in concept will allow fewer nursing personnel to supervise more patients and provide better patient care at less cost per patient. At the same time a plea must be made that the support services for the emergency department either be within the area or immediately adjacent. This is most true of the radiology department and the laboratory with the blood bank. It would be ideal if these facilities were adjoining the emergency department as well as the surgical suite and delivery areas. Patient handling would be at a minimum, and in the event of a disaster with impaired electrical service, not being forced to depend on elevators would be of great benefit. Also, the proximity of these support facilities will reduce the time a patient spends in the hospital from the time he or she enters until departure. Even though the bulk of the time is spent being pushed from the radiology department to the laboratory and back again, in the patient's mind the excessive time spent is due to the inefficiency of the emergency department. However, it is unfortunately cheaper to build vertically rather than laterally.

Recent developments

There have been several recent developments in the provision of outpatient medical care that are conducive to improved patient care and reduced patient cost. These are the ambulatory care centers, holding wards, and surgicenters.

Ambulatory care center. The ambulatory care center is not a new idea but rather a logical extension of the triage concept. It is well established that the majority of patients seen in the emergency department are not true emergencies, and in effect the patient is looking for medical care that he perceives is unavailable to him otherwise. The shifting of people around the country as well as the decrease in the number of family physicians has caused many patients to seek their medical care from the most readily identifiable source, the hospital. Indigent patients also come to the emergency department because they can get treatment for several membtrs of the family at one time, avoiding the clinic

route that may require visits at different times and on different days for different members of the family. To avoid saturating the emergency department with these nonurgent cases, some medical centers have established areas to provide these patients with temporary care and then referral to either the proper physician or a clinic. These ambulatory care areas are most useful if staffed in the late afternoon and evening when the load of emergency patients also increases. Referral to these care areas is usually done by the emergency department triage nurse. The ambulatory care area is staffed by family practice physicians or moonlighting house officers.

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A brief comment should be made about triage nurses and emergency department nurses in general. The growth of the emergency department has not only forced the development of a new type of physician but a new breed of nurse as well. Nurses working in emergency departments have moved into activities that only a few years ago would have been considered solely within the province of a physician. By training and experience, the nurse has become adept at cardiopulmonary resuscitation, defibrillation, and pulmonary control as well as splinting and bandaging, thereby extending the physician's services considerably. It has been this type of nurse, more sophisticated medically, who has been given the responsibility of evaluating the patient initially and directing him into either the emergency department or the ambulatory care area. The emergency department nurse is now also expected to initiate care for patients as a part of the triage by ordering x-ray films or laboratory tests before the physician sees the patient. The Emergency Department Nurses Association (EDNA) was chartered in December, 1970, as an organization more responsive than general nursing associations to the needs and aspirations of emergency department nurses. The growth of the association has been rapid. (Most appropriately the symbol of the group is a "road runner.") This organization now uses the staff and office structure of the ACEP.*

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Holding wards. The holding ward within the emergency department is basically also a development of what was already being done in patient management. Certain classes of patients not really sick enough to be admitted, asthmatics in whom it was hoped the attack could be quickly "broken" or children in an acute, painful, sickling crisis who were expected to be relieved of the pain fairly quickly, have been kept and observed by the emergency department personnel in examination or treatment rooms. Patients with very mild symptoms who might have an intra-abdominal problem and who will need reevaluation in a few hours have also been kept for observation in the emergency department. Actually if the emergency department is not too busy, and especially in a hospital without house staff coverage, better observation can be maintained

*In October, 1972, it was decided that the interests of the ACEP and the UA/EMS as well as the Society for Critical Care Medicine could better be served by a confederacy. The office and managerial staff of the ACEP has been delegated the organizational activities for all three associations.

in the emergency department than could be provided on the hospital floor. With the ever-increasing cost of hospitalization, if only a few hours of watching are needed, it seems wasteful to admit such patients and force them to pay a full day's charges.

Keeping such patients in the emergency department resulted in examination rooms that were tied up for a long time, and moreover, treatment rooms lacked toilet facilities and dietary service. The remedy has been the development of holding areas of 5 to 10 beds within the emergency department but with their own supervisory nurses. A holding area without its own staff nurses would be a detriment to patient care because the chances would be great that the emergency department nurses would not be able to keep watch on these patients as well as perform their other duties. In large metropolitan hospitals that treat many alcoholic patients for head injuries, holding wards run the risk of becoming "drunk tanks," but these patients as much as any others deserve proper medical observation and care. Usually the holding ward beds are cleared at 8 or 9 A.M., the decision being made at that time either to admit or send the patient home.

Surgicenter. The surgicenter concept began several years ago in Phoenix, Arizona,[16] when a group of physicians decided that they could send patients home after some operations wherein a general anesthetic had been administered if these patients were kept in a recovery area until fully stabilized. By this mechanism the patient comes to the surgicenter fasted, has his anesthetic and operation, is watched until he has recovered his normal physiologic state, and then is taken home. Since these centers are outside of the hospital with built-in costs of special care and service areas, the cost per procedure is less than if it were done on an inpatient basis. It has been suggested that the same sort of service could be provided by a hospital in conjunction with the outpatient area and using the holding ward beds for observation. This might be feasible if there was good cooperation between the personnel of the surgicenter as well as with the emergency department; otherwise it might work to the detriment of both. The idea is attractive in the sense that it tends to ensure the maximal use of all the facilities; also, the holding ward is usually least occupied at the times when a surgicenter would be in full swing.

EMERGENCY MEDICAL CARE SYSTEMS

Only a few areas of the United States have developed the facets of emergency medical care well enough to warrant being called a "system." The best known of these is Jacksonville, Florida, including Duval County; with funding from the Emergency Medical Services Programs, Department of Health, Education, and Welfare, the program is being extended to adjacent counties.[23] Many articles have appeared in both the medical and lay press about the advances achieved in Jacksonville, and much of the credit must go to Captain John Waters (United States Coast Guard, Retired) in his position as executive assistant and operating officer, office of the mayor, for the city of Jacksonville. He worked with the local medical authorities to develop a program to handle heart attack victims on the scene as well as victims of trauma. As a result, his trained personnel have performed defibrillation successfully on about 30% of heart attack and trauma patients.[8] Part of the success of the system is that with every call for emergency medical service, a fire department pumper is dispatched, and these

crews can arrive on the scene in approximately 2 min.[19] These firemen have been trained in mouth-to-mouth and bag-mask resuscitation and can perform closed chest cardiac massage to keep the victim alive until the life-support ambulance and crew can arrive. The system has been developed to take the patient to the most appropriate hospital for his problem after radio consultation with a physician. The ambulances of the Jacksonville Fire Department are of the demountable box type erected on a truck chassis. There is a nearby naval air station where standby helicopters are available.

Other cities such as Miami, Seattle, Los Angeles, and Houston have emergency services considerably better than what is available throughout most of the United States. These cities have developed patient monitoring and cardiac defibrillation, but the whole system is not as yet fully integrated.

Only Illinois has a statewide program in operation. Under the leadership of Boyd and Flashner,[11] a program to improve the handling of trauma patients was initiated. Hospitals in the state have been categorized as to their emergency capabilities. Regional hospitals, mostly university centers, have been established, and both areawide and local trauma center hospitals have been designated. Ambulances and training programs have been supplied in this system and have provided improved patient care; the established referral system for the more complicated problems has effected rapid patient transfer to the facility best able to furnish care. Helicopters from military bases as well as those used by the Toll Road and Highway commissions are used in these transfers. An example of the cooperation that can be achieved across state boundaries has been the naming of Washington University Medical Center in St. Louis, Missouri, as the regional (university) hospital for Illinois Trauma Region no. 4, the counties in Illinois adjacent to St. Louis.

An innovation in the Illinois plan has been the appointment of a trauma coordinator in each area. This coordinator has the knowledge to effect rapid patient management and transfer if needed. Evaluation of the results to date has indicated a decrease in the highway mortality, probably mostly a result of taking the patient initially to the hospital best equipped for his care and also of prompt transfer to the regional center of patients who require more sophisticated care.[10] This has prevented the deterioration in the patient's condition that usually resulted from delays while arranging for a bed in another institution, and then trying to find an ambulance that could carry the patient, along with the time necessary for the trip itself. The trauma coordinators also have the responsibility of training the general public as well as ambulance and hospital personnel; by this mechanism they have been able to spread information about the program and how to achieve ready access for emergency medical care.

The state of Illinois was awarded a contract from the Emergency Medical Services Program to expand the existing trauma system into a statewide total emergency medical service system in order to serve as a model for statewide systems elsewhere. Arkansas was also awarded money to try and develop an emergency medical services system in a state lacking many of the fundamentals of medical care. Arkansas has a poor distribution of physicians so that many of the rural areas have neither a doctor nor a hospital. Training programs for emergency personnel will be developed as well as communications between ambulances, hospitals, and other personnel locations. Money was also awarded to

seven counties in southeast Ohio and to Baltimore, Maryland, to upgrade the existing emergency medical services. All of these five funded projects are designated to serve as guides to help other states and communities in upgrading their own emergency medical capability.[20]

A recent series of articles in the *Medical World News* deplored the lack of proper emergency medical services. The series ended with the article, "The Tools are Here, Who is Going to Pick Them Up?"[33] Certainly the knowledge as to what constitutes proper emergency care is available. It has been well documented that many lives are lost in highway accidents because of improper handling.[18] It is equally well known that many heart attack victims die with salvageable hearts.[22] The systems of emergency care that are beginning to be developed indicate that some physicians and laymen are starting to work together to improve medical services. The public is slowly becoming informed through the efforts of insurance companies such as Employers Mutual of Wausau and through the activities of state and local medical societies. It has been the dedicated task for many years of the Committee on Trauma of the American College of Surgeons as well as of the Committee on Injuries of the American Academy of Orthopaedic Surgeons to upgrade emergency medical services. The results of all these efforts may be that the long night is ending, and we are beginning to see the dawn of the day when systems for emergency medical care will be available throughout the United States. A finer opportunity will never be presented to physicians to fulfill their aims of saving life and reducing disability than is afforded in the development of such a system in their own communities.

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2

Emergency management of facial fractures

ROBERT F. RYAN
FREYDOON DEJKAMEH

"Fractures of the face, although they are not frequent, nevertheless are much less rare than we have thought and most of them are not discovered by the physician." Although written in 1900 by LeFort, this statement is almost as true today as it was then.[5]

Providing an adequate airway and controlling hemorrhage are the major emergencies associated with facial fractures. (Shock, when present, is usually a result of other injuries and not just the facial fractures.) Few patients die from the fractures per se, but instead die from associated head or neck injuries or airway obstruction. The latter may result from mandibular fracture with a loss of the support necessary to hold the tongue forward, especially in the unconscious patient. A second cause of obstruction is foreign matter such as chewing gum, tobacco, dentures, and blood clots in the airway. If a patient is unconscious on arrival at the emergency room and shows any evidence of airway obstruction, it is imperative that the mouth be opened, the tongue pulled forward, and the throat cleared of foreign material. With the mouth held open, insertion of the index finger is the best way to clear the upper airway. If this maneuver and the placement of an oral airway does not solve the problem, a laryngoscope is then used to check the airway. The third cause of airway obstruction is laryngeal and tracheal injury. Laryngeal fractures are seen with increasing frequency, and with submucosal hemorrhage and edema, obstruction can result. If an endotracheal tube cannot be inserted through the glottis, then tracheotomy is indicated. Schultz,[7] however, reported that tracheotomy was only necessary in 8 of his 1042 patients with facial injuries.

Bleeding from facial fractures can usually be controlled by simple tamponade. Occasionally, maxillary fractures with a free-floating hard palate will be associated with severe hemorrhage from the internal maxillary artery and the

palatine vessels. Emergency intubation and suture ligation of the vessels is then necessary.

Case I. W. C., a 19-year-old white female, arrived at Charity Hospital emergency room approximately 2 hr after being in a car accident. Patient was a passenger in the front righthand seat and did not have her seat belt fastened.

The patient had a laceration lateral to the left eye and an extensive laceration from the upper lip down over the angle of the mandible on the left. The patient also had fractures of the left radius and right ankle.

Examination for facial fractures revealed fractures of the mandible, a LeFort III fracture on the left with the left zygoma and malar complex involved, and a free-floating palate on the left with bleeding from the posterior palatal area. During the patient's work-up in the accident room, her hematocrit dropped from 38 to 22. The rest of the physical examination and laboratory studies were within normal limits.

Two units of blood were administered and a cuffed oral endotracheal tube was inserted with the patient awake. The patient was taken to the operating room where a tracheotomy was done. The head and neck were prepped and draped for definitive surgery. With manipulation of the palatal fractures the bleeding became more brisk and it was necessary to suture ligate the left palatine artery and a branch of the internal maxillary artery. The patient required a total of six units of blood and 2000 ml of Ringer's lactate. The fractures were stabilized with direct interosseous wire and suspension wires as described by Adams,[1, 2] a Kirschner wire from the left malar bone to the right malar bone, and sections of arch bars attached to the remaining teeth.

Reduction of the ankle and wrist fractures was accomplished by the orthopedic service.

This patient also presented another problem. A chest film was obtained in the recovery room because we were concerned about the amount of blood aspirated by the patient prior to intubation. The chest film revealed left pneumothorax that required a chest tube to keep the lung expanded.

With the establishment of an adequate airway, control of hemorrhage, and location and treatment of the cause of shock completed, one may then begin the diagnosis and care of facial fractures in an orderly sequence.

Facial trauma is still one of the commonest causes bringing patients to the accident room. While less than 50% of these patients will have associated facial fractures, many of those with fractures are missed today as they were in LeFort's time. Malar fractures are frequently overlooked and found only when the edema subsides, a week or 10 days after the injury. In reviewing the charts of patients where the facial fracture was initially missed, the physicians treating the patient in the accident room were either distracted by the overlying laceration or were so occupied by other, more obvious injuries such as compound fractures of the extremities that they did not note the facial fractures.

CLASSIFICATION OF FACIAL FRACTURES

Many different classifications have been suggested for facial fractures. We favor either the one by Schultz[7] or that of Berggren.[3] Schultz uses the concept of upper, middle, and lower face, whereas Berggren's classification is slightly different. The two classifications are listed below.

Location of fracture according to Schultz[7]

1. Upper face
   a. Frontal bone
   b. Frontal sinuses (glabella)
   c. Supraorbital ridge
2. Middle third of face
   a. Nasal bones and septum

b. Maxillary sinuses (antrum)
c. Orbital bones
d. Zygoma
e. Zygomatic arch
f. Maxilla
   (1) Transverse (LeFort I)
   (2) Pyramidal (LeFort II)
   (3) Cranial facial dysjunction (LeFort III)
g. Alveolar process
h. Maxillary dentition

3. Lower third of face (mandible)
   a. Mandibular dentition
   b. Alveolar process
   c. Symphysis
   d. Corpus or body
   e. Angle
   f. Ascending ramus
   g. Condyle
   h. Coronoid process

Classification of facial fractures according to Berggren[3]

1. Nasal
2. Mandibular
3. Lateral midface (zygomatic-malar); including:
   a. Zygomatic arch
   b. Orbital floor (blow-out)
4. Midface
   a. Low transverse (LeFort I)
   b. Pyramidal (LeFort II)
   c. Craniofacial dysjunction (LeFort III)
5. Complex—combination of above

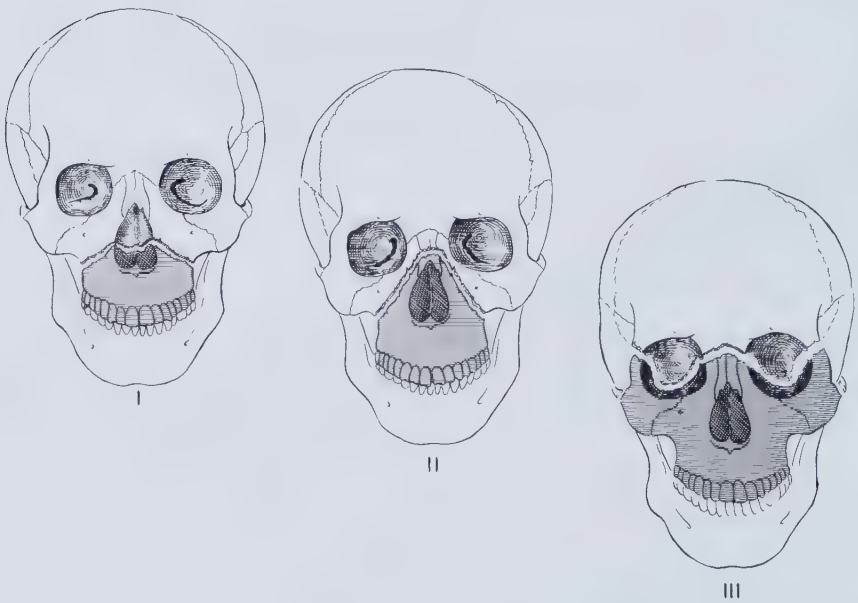

Fig. 2-1. Illustrating classic LeFort I, II, and III fractures.

Although either of these classifications can be used to describe the *location* of the fracture, the *type* of fractures are named according to the scheme employed with those found in any bones. Thus the fracture will be closed or open, green-stick or comminuted, impacted or nonimpacted, and displaced or nondisplaced. Facial fractures are more commonly open or compound than fractures elsewhere in the body. While broken facial bones rarely protrude through the skin to become compound, they frequently are exposed through the mucous membranes of the oral, nasal, or sinus cavities and are properly classified as open or compound fractures. Fig. 2-1 illustrates the classic LeFort I, II, and III fractures.

CAUSE AND FREQUENCY OF FACIAL FRACTURES

In studying 1042 patients with facial injuries, Schultz listed the automobile as the most common cause (Table 2-1). Schultz lists the most common facial bones broken as (1) the nose, (2) the zygoma, (3) the mandible, and (4) the orbital floor (Table 2-2).

Our experience at Charity Hospital in New Orleans would indicate that mandibular fractures are second in frequency and zygomatic or malar fractures third. Such differences in incidence are readily explained by Dingman and

Table 2-1. Causes of facial injury*

Cause	Number of patients	Percent
Automobile accident	565	54
Home accident	171	17
Athletic injury	118	11
Animal bite	60	6
Other	55	5
Intended injury	46	4
Work injury	27	3
Total	1031	100

*From Schultz, R. C.: Facial injuries, Chicago, 1970, Year Book Medical Publishers, Inc.

Table 2-2. Frequency of facial bone fractures*

Type	Number	Percent
Nasal bones	382	37
Zygoma and arch	159	15
Mandible	112	11
Orbital floor	112	11
Maxilla	84	8
Teeth	71	7
Sinuses	50	5
Supraorbital	36	4
Alveolus	25	2
Total	1031	100

*From Schultz, R. C.: Facial injuries, Chicago, 1970, Year Book Medical Publishers, Inc.

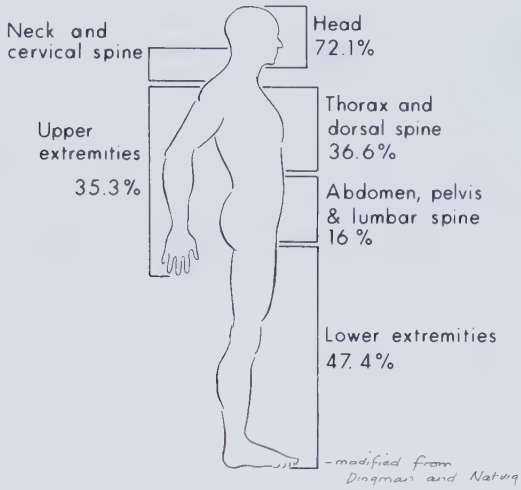

Fig. 2-2. Listing of injuries in other areas of body from transportation accidents associated with head and neck injuries.

Natvig[5] in the following statement: ". . . reports from large metropolitan emergency hospitals serving highly transient, relatively low income social groups show that a great percentage of facial fractures are caused by the impact of fists or weapons. On the other hand, hospitals in areas of higher socio-economic level report more facial fractures resulting from transportational and recreational accidents." Dingman and Natvig also point out the association of injuries of the head and neck area with injuries of other areas of the body in transportation accidents (Fig. 2-2).

These differences in the incidence of various types of fractures are pointed out to emphasize that the history of the injury is helpful in alerting the physician as to the type of fracture his patient may have.

LOOK, LISTEN, AND THEN TOUCH

The dictum of "look, listen, and only then touch" is especially important when dealing with facial trauma. If the patient arrives at the emergency room within a few minutes of the accident, before massive swelling has developed, many facial fractures are readily visible. Malar fractures are often seen from the head or foot of the examining table much more readily than from directly over the patient (Fig. 2-3). Looking at the patient and noting any asymmetry should not require more than a few seconds.

While looking at a patient, ask about the accident, how the patient was struck, with what, from what direction, etc. If the patient was in an automobile accident, where was he riding, and were seat belts and shoulder harnesses fastened? The state of consciousness can now be assessed. If the patient is conscious, check for gross visual acuity and eye movements.

Having looked at and listened to the patient, we now touch and examine for specific facial fractures. The most important part of this examination is to establish a routine and always follow the same routine to avoid missing facial frac-

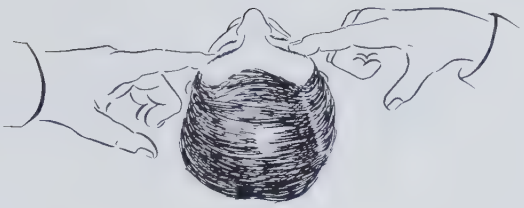

Fig. 2-3. Depicting depression of left malar bone, which is often more readily visible from head or foot of table rather than observing full face.

Fig. 2-4. Showing palpation of entire calvaria for lacerations and fractures.

Fig. 2-5. Showing palpation of superior orbital rim.

Fig. 2-6. Showing palpation of inferior orbital rim.

tures. We prefer to place both hands on the scalp and gently feel the entire calvaria for hidden lacerations and depressed fractures and to locate particles of glass, etc. that might be present.[4] The small depressed fracture that is palpable a few minutes after the injury will often not be palpable after an hour or two. In palpating for skull and facial fractures (Fig. 2-4), seek the classic findings of any fracture: point tenderness, deformity, crepitation, or abnormal motion.

Next, with the hands supporting each side of the head and face, palpate the orbital rims with the index fingers (Figs. 2-5 and 2-6), starting superiorly and progressing around the entire rims. Look for conjunctival hemorrhage and again check eye movements and gross visual acuity. If you start medially and go

Fig. 2-7. Examination for fracture of nasal bones and abnormal motion.

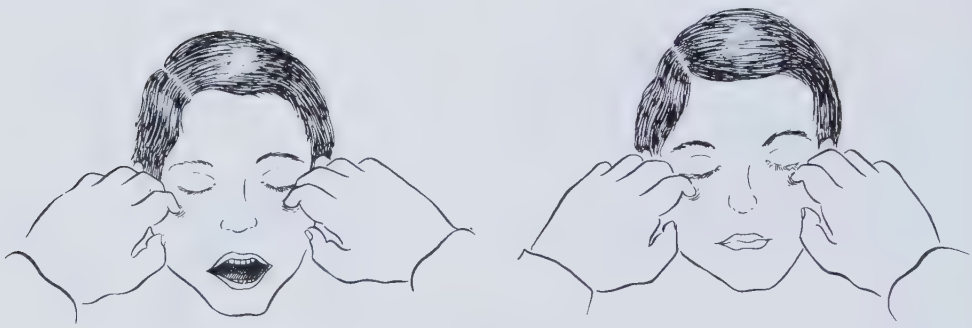

Fig. 2-8. Showing palpation along zygomatic arches.

Fig. 2-9. Showing palpation along inferior and posterior margin of mandible.

Fig. 2-10. Examination of mandible for submucosal hemorrhage and abnormal motion.

laterally over the superior rim, you then end up medially with both hands and can readily check the nose (Fig. 2-7). In addition to palpation, gently chuck the nose for abnormal motion. If a nurse or aide is present, ask for a nasal speculum and otoscope. While these are being obtained, complete the rest of the examination.

Palpate the malar eminences (Fig. 2-8) and run your fingers out along the zygomatic arches while the patient tries to open and close his mouth. Fractures of the zygomatic arches, condyles, or coronoid process of the mandible are usually discovered by these maneuvers.

Next pass your index fingers over in front of the ears and palpate the ascending rami of the mandible. Then slide your fingers down and back to the posterior edge of the mandible and then along to the symphysis (Fig. 2-9). Again, if the patient is conscious, have him slowly open and close his mouth while examining the mandible. Look at the patient's occlusion. Ask if his teeth seem to fit right on "setting" his teeth. Malocclusion is often the best sign of a mandibular or maxillary fracture. Next you need to perform the intra- and extraoral examination of the mandible (Fig. 2-10). You should look for tears in the mucosa or submucosal hemorrhage that will often identify the fracture site. Having finished examining the mandible, the maxillae should be checked for abnormal motion (Fig. 2-11).

By now the nurse will have returned with the nasal speculum and otoscope. Examine the nasal septum for lacerations and submucosal hemorrhage as well as for displacement. If there is clear fluid dripping from the nose, check it with urine sugar test sticks. Cerebrospinal fluid contains sugar and will give a positive reaction, whereas normal nasal secretions contain mucus and no sugar and thus will give a negative reaction. Also check the ear canals for the presence of bleeding or spinal fluid loss.

While this discussion is primarily limited to facial fractures, any patient with facial trauma must be suspected of having central nervous system injury. Following the state or level of consciousness is most important, and neurologic examination is indicated. In addition, every patient with facial fractures should be checked for cervical spine injuries. If the injury is serious enough to warrant obtaining skull films, then cervical spine films may also be obtained. Paraplegia or even quadriplegia resulting from a missed cervical spine fracture is a catastrophe

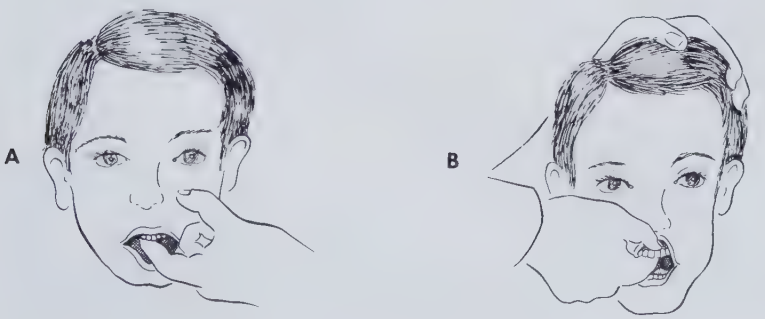

Fig. 2-11. Examination for fractures of upper alveolus. Abnormal motion will be detected in most cases of LeFort II and III fractures.

that must be prevented. It can only be avoided if we are aware of the possibility and take due precautions.

While a great deal of time and space has been devoted to the discussion of the examination of the patient for facial fractures, the actual examination as outlined can readily be accomplished in less than 2 min. This is a small price to pay to avoid missing facial fractures.

ORDERING X-RAY FILMS

Having made a clinical diagnosis of a facial fracture in a patient on the basis of looking, listening, and examining him, any decision concerning x-ray films to be taken depends on the circumstances. If the patient is unconscious, in shock, or has other serious injuries, it may be wise to delay facial x-ray films and direct all your attention to the other injuries. The majority of facial fractures can safely be noted and observed for 1 to 2 weeks before definitive treatment is undertaken. Certainly if massive edema is already present such a delay is indicated. Moreover, if other injuries contraindicate moving the patient to the radiology department for films taken by a competent technician, delay taking the films. Films taken on a portable machine in the middle of the night by the newest student technician on call are usually a total waste when dealing with facial fractures.

Assuming the patient has no associated injuries what x-ray films should be ordered? We have found the checklist shown below to be of help in teaching interns and residents.

Checklist of x-ray films for facial fractures

1. Nasal fractures
   a. Lateral view of nasal bones
   b. Occlusal view of nasal bones
2. Mandibular fractures
   a. Posteroanterior view of mandible
   b. Oblique view of mandible
   c. Occlusal view of mandible
   d. Towne's view of condyles and ascending rami
   e. Panorex x-ray films of mandible
3. Lateral midface (zygomatic, malar, zygomatic arches)
   a. Water's (occipitomental) view
   b. Reverse Water's view
   c. Tangential view of zygomatic arch
   d. Lateral view of facial bones
4. Midface (low transverse [LeFort I], pyramidal [LeFort II], craniofacial dysjunction [LeFort III])
   a. Water's view
   b. Reverse Water's view
   c. Lateral view of facial bones
5. Complex (combinations of above)
   a. Water's view
   b. Reverse Water's view
   c. Lateral view of facial bones

In addition to these x-ray films, laminagrams are often helpful in suspected blow-out fractures of the orbit. A true blow-out fracture is defined as a fracture of the floor of the orbit with herniation of orbital contents down into the maxillary sinus without evidence of fracture of the orbital rim. This fracture is caused by a blow

to the eye, as with a golf ball, that does not hit the orbital rim before striking the globe. Diplopia or limitation of eye motion is usually present as noted in the case history that follows:

Case II. A. B., a 16-year-old white male, was attacked and robbed on September 13, 1973. After being knocked to the ground, he was kicked in the left side of his face.

When seen at Charity Hospital 24 hr later, he had marked swelling and ecchymosis of and around the left eye. Vision was normal, but upward gaze was limited on the left side. The orbital rim was intact and no fractures were palpable on physical examination. Radiologic examination revealed a blow-out fracture with opacification of the left antrum and air in the orbital cavity (Fig. 2-12).

After the swelling had sufficiently subsided (6 days later), the patient was taken to the operating room and the floor of the orbit was explored. Trapped tissue was freed and a small disk of thin Silastic was sutured over the defect in the orbital floor.

In general, the best single x-ray film to order with facial fractures is Water's view. If there is extensive facial damage with some respiratory problems, the reverse Water's view should be obtained to avoid turning the patient.

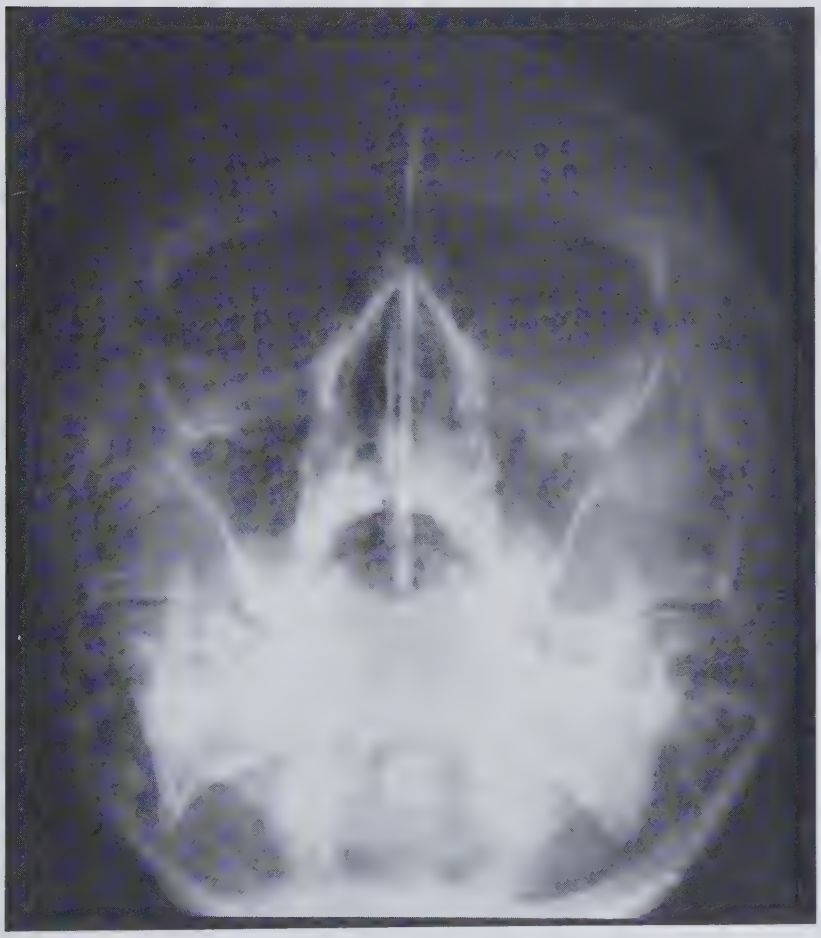

Fig. 2-12. X-ray film showing blow-out fracture with clouding of left antrum.

EMERGENCY ROOM TREATMENT AND DEFINITIVE SURGERY

Assuming the patient does have a facial fracture that has now been confirmed by appropriate x-ray films, what treatment should be attempted in the emergency room? If the patient has limited soft tissue injuries such as lacerations or abrasions, they can be treated. If the patient has a simple nasal fracture, this can often be readily reduced in the emergency room.

Local anesthesia is used as follows: applicator sticks are dipped in equal parts of 4% cocaine and 1:1000 epinephrine (Adrenalin). These are wrung out and then placed in a position to anesthetize the nasal ciliary and the sphenopalatine ganglion. One is advanced along the floor of the nose in the lower concha straight toward the back of the throat, and then pulled forward approximately ½ to 1 inch to block the sphenopalatine ganglion. The next applicator is placed to form a 60-degree angle with the first and then drawn up toward the inner canthus of the eye in the upper concha to block the nasal ciliary ganglion. These are left in place on each side of the nose for approximately 3 to 4 min. After removing the applicator sticks, three fingers of cotton soaked and wrung out in the same solution are then placed to fill the entire cavity of the nose to assure good anesthesia of the mucous membranes.

On the outside of the nose, local anesthesia is used to block the infraorbital nerve and the trochlear nerves at the top of the nose as well as the ethmoid and septal branches of the nose at the nasal spine.

Once this has been done and there is good anesthesia of the area, various instruments can be used to straighten the septum or to elevate the fractures. Once these have been snapped into position, a small plaster of paris splint is applied and packing placed in the nose. The packing can usually be left for 3 to 5 days. The splint should be worn for at least 7 days; if there is moderate swelling, it may have to be changed at this time. In a humid climate it is advantageous to apply the splint directly on the skin rather than to apply it over tape.

Similarly, if the patient has a simple, closed, and nondisplaced fracture of the mandible, Erich arch bars or Stout wires may be applied and the patient treated on an outpatient basis.[6] It is often possible with certain fractures, depending on their location and the stability, to use intramaxillary fixation by putting wires around the two adjacent upper teeth and placing separate wires around the two opposing lower teeth and then twisting these wires together. This is the method advocated for so many years by Dr. Kazanjian. In other cases where there are multiple fractures, it is necessary to use either Stout wires or Erich arch bars. Figs. 2-13 and 2-14 show how these are applied.

If the patient is unconscious, it is safest to apply wires or bars and wait until the patient is fully conscious and not nauseated before fastening rubber bands between the upper and lower set of teeth. With the hooks of the Erich arch bars or the loops that are left exposed with a Stout wire, one can apply rubber bands whenever it is convenient in order to realign the fractures.

If, however, the fractures are compound, displaced, and complicated by extensive soft tissue injury, the patient should be admitted to the hospital and appropriate treatment carried out in the operating theatre under proper conditions to ensure the best possible results. The technique of open reduction and internal fixation as initiated by Adams[1, 2] has become the treatment of choice

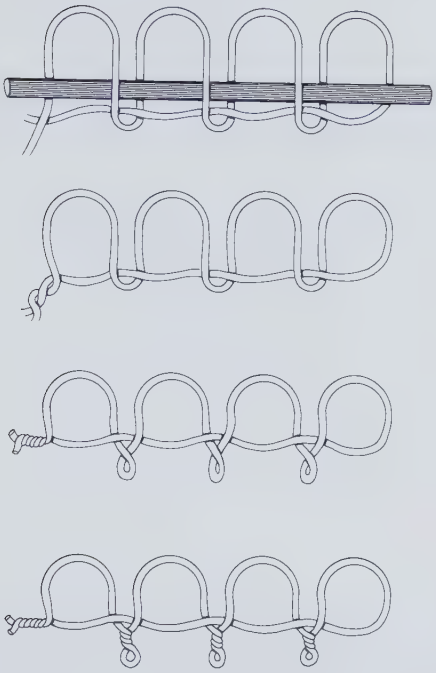

Fig. 2-13. Showing method of applying Stout wires. Malleable brass shown at top is removed and wire twisted to form loops over which rubber bands can be hooked.

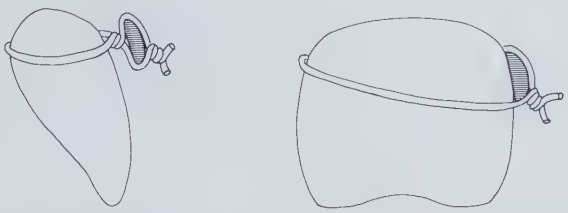

Fig. 2-14. Application of Erich arch bars. The half twist in wire before putting around arch bar is applied for canine teeth, but direct wiring is done on molar teeth.

for most facial fractures. Often the soft tissue injury will be debrided and sutured in the emergency room, the patient started on appropriate antibiotics and tetanus prophylaxis, and, when indicated, a temporary splint applied. The patient is then admitted and the operation is carried out later, depending on local conditions.

The third most common fractures at Charity Hospital are those involving the malar bone and zygomatic arch (Fig. 2-15). These are treated in the operating room. Because many of these patients sustain their fractures in fights and they are quite belligerent, it is much more expeditious to use a general anesthetic than it is to do the surgery under local anesthesia.

With the patient surgically prepared and draped, we explore two areas for reducing the trimalar fracture. The first incision is made over the lateral orbital rim. This incision is short, approximately 2 cm long, and depending on the loca-

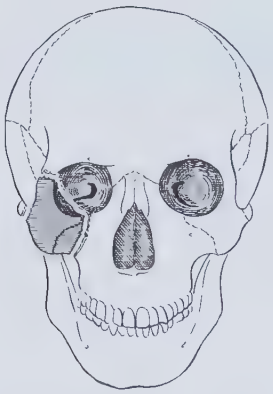

Fig. 2-15. Trimalar fracture.

Fig. 2-16. **A,** Eyebrow incision retracted to show fracture in lateral orbital wall. **B,** A 26-gauge stainless steel wire has been placed through drill holes and twisted to reduce the lateral orbital wall fracture. **C,** Orbital contents are being elevated by ribbon retractor, and a thin sheet of Silastic to replace the orbital floor is seen just above lower rim of bone. Silastic sheet was sutured in place to periosteum. Wires are also shown. **D,** Patient after debriding and resuturing forehead wound and closure of the two orbital rim incisions.

tion of the eyebrow the incision is made on the undersurface of the eyebrow overlying the orbital rim (Fig. 2-16, *A*). This fracture can usually be palpated and is relatively close to the suture line of the lateral orbital wall. The bone is exposed, and if there is separation of the fracture at this area, small drill holes are made and 26- to 28-gauge stainless steel wire is used to secure these fragments.

Next an incision is made in the lower eyelid over the infraorbital rim (Fig. 2-16, *A*). The fracture is easy to palpate, and the stair-step feature is usually present in displaced malar fractures. Some physicians prefer to make an incision at the lid margin much as they would a blepharoplasty incision. We prefer to make the incision at the lower part of the lid over the orbital rim. This incision is 2 cm in length. It can be extended either medially or laterally, depending on the fracture site. The incision is slightly curved and in time gives an excellent cosmetic result. It is carried down to the bone, the periosteum is reflected, at the two sides of the fracture the drill holes are placed through the bone, and a small wire is put through. Usually 26- to 28-gauge stainless steel wire is sufficiently strong for wiring these fractures.

In order to reduce the malar fracture, a curved instrument can be introduced through the superior incision at the outer rim of the orbit. The instrument is advanced under the arch of the malar bone and the reduction is accomplished. We found it useful to have the drill holes placed through the fragment sites and wires put through, and then as the fragment is elevated into position these wires can be tightened to secure the fragment in the new position (Fig. 2-16, *B*).

At times, because of the angle of the fracture, it is difficult to maintain the position of the malar fragments. It may be necessary to use a Kirschner wire threaded through the malar bone from the outside, passed through the nasal cavity, and advanced into the opposite malar bone to stabilize the fracture. It is well to remember that one must have an oral endotracheal tube in place, rather than a nasal endotracheal tube when passing this transfixing Kirschner wire from one malar bone to the other. If the fracture is impacted and in poor position, in order to create enough leverage to disimpact the fragment it is necessary to go up into the temporal bay of hair and make the small incision that was originally advocated by Gilles; from this area one can obtain enough leverage to free the fragment of the malar bone and elevate it into its correct position. The subcutaneous tissue in the wounds can be closed with some very fine Dexon or chromic sutures, and then running intradermal sutures of 4-0 or 5-0 monofilament nylon suture can be placed, especially in the lower eyelid incision. These can be removed whenever convenient once the swelling has subsided. Fig. 2-16, *A* to *D*, shows the steps for wiring a displaced malar fracture, with a piece of Silastic sheeting used for the floor of the orbit.

SUMMARY

Facial fractures per se rarely demand emergency care. Occasionally these fractures are associated with airway obstruction and hemorrhage, which demand immediate attention. All patients sustaining facial trauma must be evaluated for possible central nervous system damage and cervical spine injury. A simple routine examination that can be performed in less than 2 min will reveal the presence of almost all facial fractures. If not contraindicated by associated in-

juries, x-ray films can be obtained to confirm the clinical diagnosis of facial fracture. While simple, closed fractures of the nose or mandible may be cared for in the accident room, the majority of facial fractures should be repaired under ideal conditions in a properly equipped operating room.

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3

Cancer chemotherapy: practical comments on current techniques*

GEORGE J. HILL II

Surgeons are naturally concerned about the long-term results of their procedures and have a particular awareness of the limitations of conventional surgery and radiation therapy in treating many patients with solid tumors. Although the results vary considerably from one hospital to another, it is obvious that the salvage rate among patients with the common solid tumors is no better than 50%, and mortality in carcinoma of the lung approaches 90%. Results are better in patients with small localized cancers, but unfortunately the diagnosis is often made only when the patient appears with advanced disease. The role of surgery is often palliative rather than curative. Benefits are seen from surgery and radiation therapy in the treatment of local lesions, but systemic therapy is obviously the best theoretic means for therapy of disseminated neoplasms.[11, 14, 15, 124] The thoughtful use of new drugs[109] and hormones[7] by cancer chemotheraptists has demonstrated the effectiveness of chemotherapy in properly selected patients. The next decade will see the increasing application of cancer chemotherapy by internists who specialize in medical oncology in treating disseminated solid tumors. However, at the present time the knowledge of the natural history of the solid tumors and the access to patients with these tumors are mainly in the area of general surgery, so surgeons will still be called on to consult and treat many of these patients. For this reason guidelines in the current concepts of cancer chemotherapy should be understood by surgeons.

This discussion is based on experiences with approximately 700 patients with

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advanced cancer treated at the University of Colorado and Washington University School of Medicine between 1967 and 1973.[52, 53, 56]

STANDARD AGENTS

More than two dozen different drugs and hormones are commercially available at the present time that have well-documented antineoplastic effects. Many of these agents are similar; in other cases the effects are either limited primarily to the leukemia-lymphoma neoplasms or are of relatively little benefit in treating human cancer. It is therefore reasonable for the general surgeon to be thoroughly knowledgeable about only a few of the cancer chemotherapeutic agents and to understand the rationale, indications, dosages, routes of administration, and toxicity of each of these drugs.

The drugs most useful in the treatment of solid tumors are the antimetabolites 5-fluorouracil (5FU) and methotrexate (MTX); nitrogen mustard (HN2) and its derivatives such as cyclophosphamide (Cytoxan), melphalan (Alkeran), and chlorambucil (Leukeran); the antibiotic actinomycin D (dactinomycin); the mitotic inhibitors vincristine (Oncovin) and vinblastine (Velban); and four classes of hormones—the corticosteroids (prednisone), estrogens (diethylstilbestrol [DES and Stilphostrol] and chlorotrianisene [Tace]), androgens (testosterone and fluoxymesterone [Halotestin]), and the synthetic nonmasculinizing androgen (testolactone [Teslac] and calusterone [Methosarb]), and progesterone (Delalutin and Provera) derivatives. Each of these types of drugs has a specific indication, and useful benefit will be achieved in some patients with metastatic neoplasms. The manufacturers' package inserts should be studied carefully before these drugs are used. However, the package inserts serve only as guidelines, and it should not be assumed that the usual dose of the drug can safely be administered to all patients. For this reason, common sense and good judgment are required when administering the drugs to patients with advanced cancer.

Drugs in common use

Antimetabolites. The antimetabolites currently in common use for solid tumors are 5-fluorouracil and methotrexate.

5-FLUOROURACIL. 5FU is a competitive inhibitor of thymidylate synthetase and thus interferes with DNA synthesis. It can usually be administered safely to patients who have not had extensive prior pelvic irradiation or pancytopenia. The white count should be at least 3500 and the platelet count 125,000 or greater prior to each dose of 5FU. If this guideline is followed, therapy with 5FU can be given on an outpatient basis utilizing a "loading course" of 500 mg/day intravenously for 5 days followed by weekly doses of 500 mg each.[100] The dose can be increased gradually to a maximum of 1000 mg if the patient shows no significant drop in blood count, stomatitis, or diarrhea.[60] This method will temporarily produce partial or complete response in 15% to 30% of patients with adenocarcinomas of the gastrointestinal tract, squamous cancers of the head and neck, squamous carcinoma of the skin, and adenocarcinoma of the breast. Responses may persist for a few weeks to several years,[62, 84] although the overall time of survival may not be changed by 5FU therapy.[102]

METHOTREXATE. MTX is an antimetabolite that acts as a competitive analogue of folic acid, interfering with methylation reactions. It is important that patients

treated with MTX have normal renal function, and blood urea nitrogen and creatinine levels should be checked prior to instituting MTX therapy. If the patient becomes dehydrated or develops ureteral obstruction, fatal MTX toxicity can occur swiftly.

MTX is available in both parenteral and oral forms. The weekly injection of 25 to 50 mg intravenously is well tolerated by most patients in good condition, but the white count and platelet count should be checked before each dose (see protocol on p. 46). The white count should be 3500 or greater, and the platelet count 125,000 or greater, as with 5FU. Oral therapy (1.5 to 5.0 mg/day) can be rather easily titrated by most patients because epigastric discomfort or early stomatitis is an indication for temporary cessation of therapy.

MTX will produce responses in approximately 30% of patients with squamous carcinomas of the head and neck and adenocarcinoma of the breast. Responses are also occasionally seen in other squamous cancers.[94] If the drug is "pushed" to the limit of toxicity by experienced chemotherapists, responses may be seen in up to 60% of patients with head and neck cancer,[70] but this practice may result in temporary periods of leukopenia and stomatitis that are worrisome for inexperienced chemotherapists.

Nitrogen mustard and derivatives. HN2 (mechlorethamine, Mustargen) is the most useful agent available for treatment of pleural effusions due to metastatic cancer. This is its main role in solid tumor chemotherapy at the present time. For this use, a polyethylene catheter[86] or chest tube[36] should be inserted into the pleural space and the effusion drained as completely as possible. HN2 is then given through the chest tube in a single injection of 0.4 mg/kg mixed in 100 to 150 ml of saline solution.[65] The drug is rapidly fixed to cell surfaces and proteins by its alkylating reaction, and it is essentially entirely absorbed and inactivated within the first half hour after administration. Therefore the patient should be turned every 5 min for the first half hour so that the drug will be distributed to all aspects of the pleural surface. The chest tube is clamped during this period. After the first half hour the chest tube is placed on drainage, because the pleural effusion often reaccumulates rather rapidly as a result of the intense inflammation caused by HN2. The pleural surfaces become adherent in most patients within the next 2 or 3 days, and the chest tube is removed when drainage has decreased to no more than 100 to 200 ml/day.

In my experience almost all patients will have a moderate but definite drop in the white count within 7 to 14 days after intrapleural administration of HN2, and it is wise to check the white count at 2- to 4-day intervals until it has passed its lowest point (nadir). The rapidity with which the white count falls and then rises is a guide to the timing and dosage permissible in subsequent cytotoxic chemotherapy.

HN2 is also used intravenously in the treatment of tumors that respond to alkylating agents, for its action is swift when given in this fashion.[79] The intravenous dose is usually 0.1 mg/kg/day for 4 days followed by a 3- to 4-week rest period. The patient will experience fever and gastrointestinal toxicity during the 4 days of therapy, and heavy sedation is ordinarily required for this type of treatment. Intravenous HN2 is most commonly used at present in the treatment of the superior vena caval syndrome.

Nitrogen mustard derivatives are available that have considerably less im-

mediate toxicity and are therefore better tolerated on both inpatient and outpatient bases. Cyclophosphamide (Cytoxan) is perhaps the most widely used of these because it is available in both oral and parenteral forms. Cyclophosphamide is adminstered in daily oral doses of 50 to 150 mg, with instructions to take the drug in the morning so that all of the renal clearance is completed before bedtime, thus reducing the risk of hemorrhagic cystitis. Cyclophosphamide can also be administered intravenously in a weekly dose of 10 to 15 mg/kg, given as a slow intravenous infusion. The drug causes depression of the white count and platelet count, but it is safer to reduce the counts to lower levels than would ordinarily be permitted when antimetabolites are used. Therefore a white count of 2000 can be used as the lower cutoff point for cyclophosphamide therapy.

Alopecia is a common side effect of chronic cyclophosphamide administration and should be explained to the patient prior to the institution of therapy with this drug.

PROTOCOL: METHOTREXATE TREATMENT PROGRAM*

PRETREATMENT STUDIES

Hct	Photographs if lesions are visible
WBC	Serum creatinine
Differential	PSP excretion
Platelets	Bilirubin
Urinalysis	SGOT
Blood urea nitrogen	LDH
Chest x-ray	Serum protein electrophoresis
Tumor measurements	Prothrombin time

Abnormalities of liver function will reduce the patient to poor-risk status. Abnormalities in renal function, if mild, will reduce him to poor-risk status. If severe, the patient must not be treated with methotrexate.

TREATMENT PROGRAM

Good risk 40 to 50 mg q4 days IV
Poor risk 25 to 35 mg q4 days IV

Treatment will be continued to toxicity; then the patient will be discharged from the hospital and the dosage will be continued on a weekly basis.

If severe toxicity develops, the dosage will be reduced by 5 to 15 mg until a stable dosage program is achieved without toxicity or with mild toxicity. Then the patient will be discharged and given the dosage on a weekly basis.

DEFINITIONS OF TOXICITY

Toxicity: WBC less than 4000, platelet count less than 100,000, or nausea and vomiting (controllable with antiemetics) or stomatitis

Severe toxicity: WBC less than 2000, platelet count less than 75,000, nausea and vomiting (uncontrolled with antiemetics), or severe oral ulcerations

*Based on Lane, M., et al.: J.A.M.A. **204**:561, 1968.

Cyclophosphamide is also used in the combination chemotherapy of lymphomas and reticulum cell sarcomas in the COPP program (see protocol for COPP therapy on p. 58). When given in this manner, responses are seen in approximately 20% of patients with carcinomas of the lung (particularly oat cell cancer) and miscellaneous sarcomas. Up to 30% of patients with carcinoma of the breast respond to cyclophosphamide, and up to 80% of patients with small cell lymphocytic lymphosarcomas will show a response.

The mustards are essentially ineffective in adenocarcinomas of the gastrointestinal tract and squamous cancers of the head and neck. The other available mustard derivatives, melphalan and chlorambucil, each has a spectrum of activity similar to cyclophosphamide. The latter two drugs rarely cause cystitis and produce less alopecia than cyclophosphamide. However, they also produce less nausea, and the patient may thus inadvertently take an excessively large daily dose of either melphalan or chlorambucil. The onset of nausea usually precedes the development of dangerous pancytopenia from cyclophosphamide.

Actinomycin D. Actinomycin D is an inhibitor of DNA-dependent RNA synthesis and thus has a different spectrum of action than the antimetabolites that inhibit DNA synthesis. It has a spectrum of activity and logarithmic cytotoxicity that is similar to the mustards and is particularly useful in the treatment of embryonal rhabdosarcoma and nonseminiferous carcinomas of the testes. It is administered in doses of 1 mg/day for 5 days to adults, followed by a 4-week rest. Actinomycin D is extremely toxic, and most patients exhibit rather severe nausea and vomiting during the period of drug administration. During the rest period following each course of actinomycin D, stomatitis and alopecia commonly occur, and most adolescent and adult males will develop some degree of acne or folliculitis.[32] This can be severe and worrisome in some patients, but it inevitably subsides by the time the next course of therapy is given. Depression of the white count and platelet count commonly occurs, with the white count falling to a nadir as low as 1500. However, in patients with no prior chemotherapy or radiation therapy, fatal pancytopenia is unlikely to occur, and recovery is almost always complete.

When given as prescribed, actinomycin D will produce partial or complete responses in approximately 20% of patients with miscellaneous sarcomas, and 40% of patients with embryonal rhabdomyosarcoma and nonseminomatous carcinomas of the testes. Complete responses that are long lasting and possible cures occur in a small percentage of patients, perhaps 2% to 5% of adults with embryonal rhabdomyosarcomas and carcinomas of the testes.

Mitotic inhibitors. Vincristine and vinblastine have relatively little role as single agents in the chemotherapy of solid tumors, but their use and toxicity should be known to anyone who administers them in combination chemotherapy. These drugs are alkaloids derived from the periwinkle plant *(Vinca rosea).* Vinblastine[106] is clearly preferable and will probably gradually be substituted for vincristine because its neurotoxicity is definitely less than that seen with vincristine.[30] Vincristine and vinblastine both cause hematologic toxicity, which is similar to the results produced by other chemotherapeutic agents when given on a weekly basis.

Guidelines for the use of these drugs are similar to those as described for 5FU and MTX. When administered as single agents, the drugs are given in

gradually increasing doses as described in the manufacturers' package insert. Vinblastine can be given in doses approximately twice as large as the doses of vincristine, producing an equivalent effect on blood count and tumors, but it will produce less neurotoxicity than vincristine. Neurotoxicity may occur in any peripheral nerve and cause either pain or paralysis. The most common early manifestation of neurotoxicity is loss of the knee jerk, and the drug should be temporarily withheld when this occurs. Paralysis of the recurrent laryngeal nerve has been reported after a single large dose of vincristine. The neurotoxicity produced by vincristine may be bizarre, manifesting itself in ineffective peristalsis and abdominal bloating. It may occur as disabling painful neuritis in the fingers and toes or as peroneal palsy. Vincristine is administered as part of the COPP program* described in a subsequent section of this chapter. It is also one of the agents in the five-drug combination chemotherapeutic regimen commonly used for carcinoma of the breast.[16]

Hormones

CORTICOSTEROIDS. The corticosteroids are administered for a wide variety of indications in patients with metastatic cancers. The most commonly used drugs are prednisone, orally, and methylprednisolone, parenterally, in doses of 15 to 45 mg/day. Cortisone acetate is used for replacement therapy after adrenalectomy or hypophysectomy in doses of 25 to 37.5 mg/day. Corticosteroids are best used in short intensive courses for patients with metastatic cancer, except when cortisone is used for replacement therapy. Long-term corticosteroid therapy imposes all the risks of iatrogenic Cushing's syndrome; the benefits do not appear to warrant this therapy except in patients who have a dramatic, obvious, immediate response to corticosteroid therapy.

Corticosteroids are used as single agents or in combination in the treatment of lymphosarcomas and reticulum cell sarcomas. These hormones exert a so-called lympholytic effect in lymphomas. Carcinoma of the breast is treated either with prednisone as a single agent, testing response to hormone therapy, or in combination therapy in a five-drug program (see protocol for five-drug therapy on p. 57). Occasionally patients with a lymphangitic spread of tumors—particularly carcinoma of the breast—derive good symptomatic benefit from high doses of corticosteroids.

The synthetic steroid dexamethasone (Decadron) has a well-established role in the temporary palliation of patients with primary or metastatic cerebral tumors. The mechanism of action was once believed to be a reduction in brain edema, but this has not been conclusively demonstrated. Nevertheless, regardless of the mechanism of action, the awakening of a comatose patient when treated with 6 to 12 mg of dexamethasone is clearly a remarkable phenomenon.

The mechanism of action of the corticosteroids in chemotherapy is also somewhat uncertain. In vitro experiments demonstrate enzyme induction and both repression and derepression of DNA. The drugs clearly interfere with protein formation, as seen in patients with Cushing's syndrome. However, the specific mechanism of action in most neoplasms is still unknown at the present time. The long-term side effects of intensive corticosteroid therapy are almost as debili-

*Acronym formed from cyclophosphamide (Cytoxan), Oncovin (trade name for vincristine), procarbazine, and prednisone.

tating and as likely to be fatal as metastatic cancer. These include peptic ulcer, compression fractures, hypertension, diabetes mellitus, and psychosis. Edema, hirsutism, predisposition to infection, muscular atrophy, and electrolyte disturbances are other consequences that should be considered if the patient is placed on long-term corticosteroid therapy.

ESTROGENS. Synthetic feminizing estrogens are used in elderly women with advanced metastatic carcinoma of the breast and in men with symptomatic metastases from carcinoma of the prostate. The usual dose of DES is 5 to 15 mg/day in women and 1 to 3 mg/day in men. Responses can be seen in virtually all elderly women with metastatic carcinoma of the breast, but the frequency of response decreases in the younger age groups. The drug should not be used in premenopausal women and should be used with great caution in patients with bony metastases. The serum calcium often rises sharply to dangerous levels in these patients,[117] even when metastases are inapparent on x-ray examination. It has been suggested that estrogen therapy can be continued and benefit seen even if hypercalcemia occurs initially,[9] but it is my impression that other forms of therapy should be tried as alternatives if the patient shows signs of hypercalcemia when estrogen therapy is begun.

Most of the elderly men with prostatic cancer will also respond to estrogen therapy, but the side effects may be so troublesome as to preclude adequate doses in some of the patients. Therefore the percentage of patients who respond for long periods of time is difficult, if not impossible, to quantitate precisely.

ANDROGENS. Androgens are administered as either masculinizing or nonmasculinizing hormones. Examples of the former type include testosterone propionate or testosterone ethanate, which are available in both oral and parenteral forms. The drugs are ordinarily given as tolerated (e.g., 300 mg/week), limited by side effects or failure of response. It is usually side effects that limit the intensity of therapy, for women are often acutely sensitive regarding the hirsutism and acne produced by androgens. Edema and nausea are also limiting factors for chronic androgen administration.

The potent synthetic oral androgen fluoxymesterone (Halotestin) has been a useful drug in the treatment of carcinoma of the breast in premenopausal women. It is much easier to manage and regulate than the injectable androgens, but does require a cooperative, intelligent patient for consistent administration of the drug on an outpatient basis.

SYNTHETIC ANDROGEN DERIVATIVES. The nonmasculinizing androgen derivatives have recently been said to produce responses in 20% to 40% of postmenopausal women with metastatic carcinoma of the breast. It is my impression that the response rate may not be this high in subsequent clinical trials. However, both Teslac and Methosarb[72] are extremely well tolerated and usually are free of disabling side effects. They should be used at some time in the management of virtually all postmenopausal patients with metastatic carcinoma of the breast.[29] It seems reasonable to use these drugs in young women as well, after oophorectomy has been performed.

SYNTHETIC PROGESTERONE DERIVATIVES. Progesterone derivatives have a distinct role in the treatment of metastatic carcinoma of the endometrium, a disease that is encountered relatively rarely by general surgeons, but may occasionally be

seen because of recurrence or metastases.[66] The manufacturer's current package insert for such drugs as Delalutin and Provera should be studied carefully; the doses used are in the range of 1000 to 5000 mg/week. Therapy is usually limited by nausea and edema or the patient's unwillingness to tolerate the large number of tablets or uncomfortable injections. Dramatic benefit is occasionally seen in these patients and every effort should be made to encourage the patient to take adequate doses for a period of at least 1 to 2 months before concluding that the therapy is ineffective. Synthetic progestins are also occasionally useful in the treatment of metastatic adenocarcinoma of the kidney (hypernephroma).[7]

Less commonly used drugs

Commercially available drugs that should be utilized from time to time in the treatment of patients with metastatic cancer include the following agents: the DNA inhibitor hydroxyurea (Hydrea), the alkylating agents procarbazine (Matulane) and thio-tepa, and the antibiotic mithramycin (Mithracin).

HYDROXYUREA. Hydroxyurea appeared to have substantial antineoplastic activity in experimental animal tumors and was reported to show significant radiation sensitization in early studies with human tumors.[73] It was also reported to have significant benefit in metastatic melanoma. None of this activity in human tumors occurs frequently, but the drug remains available as a useful second line of therapy and may achieve benefits where other drugs have failed. Hydroxyurea is given in doses of 80 mg/kg every third day or 20 to 30 mg/kg daily, depending on the preference of the patient and his physician. Since hydroxyurea does not have to be administered intravenously, the drug provides a useful alternative to the antimetabolites that are available only in parenteral form. Leukopenia or thrombocytopenia may occur with hydroxyurea, but blood counts return to normal rather promptly when therapy is discontinued.

I have seen one good partial response in a patient with melanoma. I have also seen another patient with metastatic melanoma who had a partial response to radiation therapy and who subsequently was treated with hydroxyurea. He had a complete disappearance of the residual tumor, persisting for approximately 1 year.

PROCARBAZINE. Procarbazine is a drug classified with the alkylating agents on the basis of theoretic studies, although the drug's exact mechanism is unknown at this time.[116] It also is an oral agent that has a sufficiently different mechanism of action from other antineoplastic agents to make its use worthwhile for patients who have failed to respond to the other drugs. It is employed as a single agent and also in combination therapy in the COPP program for lymphosarcoma (see protocol for COPP therapy on p. 58). Therapy is usually limited by nausea, although in addition the blood count may become low, necessitating interruption of therapy in patients who have had extensive prior cytotoxic chemotherapy. In general, however, the patient will limit his own dosage because of nausea and the blood count will remain within the safe range.

The manufacturer's brochure or package insert should be consulted for guidelines for stepwise increases in therapy. The therapy is ordinarily begun with 50 mg/day and increased to 250 mg/day over a 4- to 5-week period. Procarbazine has also been reported to be useful in the treatment of carcinoma of the lung,

PROTOCOL: THIO-TEPA DOSAGE GUIDELINES

WBC	Platelets	Thio-TEPA dose (weekly)	
		IV or IM (mg)	*Intrapleural or intraperitoneal (mg)*
6000 or over		30	60
5000-6000	200,000 or over	22	44
4500-5000	150,000-200,000	15	30
4000-4500	125,000-150,000	10	20
3500-4000	100,000-125,000	5	10
3000-3500	75,000-100,000	2.5	5
Less than 3000	Less than 75,000	Omit dose	Omit dose

Platelet and WBC count should be determined before each dose of thio-tepa is given. The more conservative dosage should usually be chosen if there is a discrepancy in dosage suggested for each of these blood counts.

although I have administered it to approximately 10 patients with various carcinomas of the lung and have seen no benefit.

THIO-TEPA. Thio-tepa is an alkylating agent of the ethylenimine type, producing a different type of alkylation than the mustard drugs. It is used in the treatment of pleural effusions and malignant ascites and also in the treatment of any of the solid tumors that respond to alkylating agents.[37] It is one of the oldest alkylating agents and has significant usefulness for several reasons. First, it is virtually free of the side effect of nausea that usually limits therapy with mustard derivatives. Second, although it is given parenterally, it is free of the vesicant effects that occur with nitrogen mustard. Third, it is prepared by being dissolved in a small volume of fluid, so that it is easily administered by a doctor or nurse, in contrast to the other common parenteral alkylating agents nitrogen mustard and cyclophosphamide. However, administration of thio-tepa requires careful monitoring of the platelet count, for this drug is virtually unique in its ability to lower the platelet count far in excess of its effect on the white count. The platelet count *must* therefore be assessed prior to each dose of thio-tepa. In general, however, the guidelines for thio-tepa dosage are based on the white count. I use the sliding scale of thio-tepa dosage outlined in the protocol above.

MITHRAMYCIN. Mithramycin has a limited but definite role in the treatment of metastatic carcinoma of the testis (nonseminomatous)[55] and in the treatment of hypercalcemia resulting from metastatic cancer.[96] This drug is usually given in slow intravenous injections of 25 μg/kg/day for 10 days, or 50 μg/kg every 2 days for a total of five doses when used in treatment of carcinoma of the testes. It is usually used in doses of 25 μg/kg for 2 to 3 days for patients with hypercalcemia. The mechanism of action on serum calcium is apparently the inhibition of para-

thyroid hormone action.[64] The effect of mithramycin on serum calcium was discovered during investigation of the troublesome coagulopathy that occasionally developed in patients treated with this drug. The main limitations on the use of mithramycin are the rather considerable nausea, vomiting, and local phlebitis produced by the drug. It is probable that other forms of chemotherapy are at least as good as mithramycin for carcinoma of the testes.[83] Specifically, actinomycin D produces as high a percentage of responses and is free of the puzzling coagulopathy produced by mithramycin. Mithramycin produces responses in approximately 25% of patients with metastatic carcinoma of the testes. Complete responses occur in 10% of patients, and a small fraction of these patients may eventually be considered cured.

EXPERIMENTAL DRUGS

The National Service Center of the National Cancer Institute has sponsored studies of more than 500,000 drugs and hormones for their effect on cancer. Of these the conventional agents already described have been found to be of sufficient effectiveness to warrant their release for commercial distribution. The toxicity of several of the drugs, e.g., MTX, mithramycin, and 5FU, has been so troublesome that restrictions or cautions are imposed on the use of the drug. Many other agents are under intensive investigation when used in human experimental studies. Some of these drugs will eventually be released for commercial use whereas others will eventually be discarded.

The experimental drugs that appear to be of the most significant benefit at the present time are described in this section. These drugs can be obtained by FDA-licensed investigators from the National Cancer Institute, which has generally been cooperative in releasing the drugs for treatment of individual patients on a humanitarian basis, on written request from a licensed physician.

Each of the drugs described in this section has specific advantages over the currently available chemotherapeutic agents, and it is believed that all of them will eventually be released for general use.

DTIC. The imidazole carboxamide derivative DTIC (dimethyl triazeno imidazole carboxamide, NSC 45388) is one of a variety of intermediary purine analogues that was synthesized for therapeutic testing. It appears to act as an alkylating agent as much or more than it acts as an antimetabolite, and it has also been demonstrated to be both carcinogenic and immunogenic in experimental animals. After nearly being discarded as ineffective, it was finally recognized as having a significant role in the chemotherapy of melanoma. At the present time DTIC is considered to be the most effective single agent in the chemotherapy of metastatic melanoma.[12, 71, 80, 121] Responses are seen in 25% of patients treated, 10% of these being complete responses. Some of these are prolonged complete responses that may eventually be considered cures.

Recent laboratory studies indicate that some patients and laboratory animals exhibit immunosuppression when treated with DTIC. However, increased tumor antigenicity has been observed in some experimental systems when tumors are exposed in vitro or in vivo to DTIC or other carboxamide derivatives.

DTIC has also been used in combination with Adriamycin in the chemotherapy of metastatic sarcomas as reported from the M. D. Anderson Hospital and

the Southwest Oncology Group. DTIC is under investigation as a surgical adjuvant for patients with melanoma who have a poor prognosis.

The usual dose of DTIC is 4.5 mg/kg daily for 10 days, followed by a 4- to 6-week waiting period to observe the effects on blood count and tumor. Nausea and vomiting commonly occur on the first 1 to 3 days of drug administration. Approximately 5% to 10% of patients exhibit a flulike syndrome at about the seventh day of drug administration. Thrombocytopenia and leukopenia usually occur in the second or third week after therapy. Many patients show a decrease in the size of metastases within the first 10 days of therapy; virtually no patients who do not show good benefit after the first one or two courses of treatment will respond to therapy with DTIC. The drug is administered intravenously and must be used shortly after it is prepared because it is unstable at room temperature.

NITROSOUREA DERIVATIVES. The nitrosourea derivatives[34, 89, 101] are a new class of alkylating agents that are chemically similar in some respects to the mustard derivatives, but also have a chemical similarity to hydroxyurea, which was discussed previously. Nitrosoureas are more highly soluble in lipids than the mustards, and this is believed to possibly account for the unusually good effect that has occasionally been seen from nitrosourea treatment in patients with metastatic brain tumors.

BCNU (bischloroethyl-nitrosourea [Carmustine], NCS 409962) is a parenteral nitrosourea that is usually administered in doses of 1.5 mg/kg daily for 5 days or occasionally in a single slow intravenous injection of 2.0 mg/kg. Patients treated with BCNU often become faint as the drug is administered, and nausea or vomiting is not uncommon for up to 24 hr. A delayed depression in blood count occurs, with a nadir in white count and platelet count occasionally occurring as late as 6 to 8 weeks after a single dose of BCNU. The reason for the profound delay in effect on blood count has not been determined; the nitrosoureas are unique in this respect among all of the cancer chemotherapeutic agents.

The nitrosoureas are used in lower doses in combination therapy with a variety of other drugs and for a variety of tumors. The main role of BCNU, however, is in the treatment of primary and metastatic brain tumors,[123] melanoma, and lymphosarcomas[128] that are resistant to conventional chemotherapy.

CCNU (chloroethyl cyclohexyl nitrosourea [Lomustine], NSC 79037) is an oral nitrosourea that probably has a spectrum of action similar to BCNU. However, the studies of CCNU in humans are not as complete as those of BCNU, and it is not certain if its effectiveness will eventually be confirmed to the same extent that the effectiveness of BCNU has been. It is available in capsules that are kept in the freezer until immediately prior to administration. The capsule is rapidly dissolved and the drug is rapidly absorbed when administered—which is fortunate, since the patients frequently vomit after drug administration. The usual dose of CCNU is 100 to 130 mg/M^2 of body surface area or approximately 2.5 to 3.5 mg/kg.

Since the nitrosoureas are often administered to patients who have received extensive chemotherapy or radiation therapy, caution should be used in selecting the dose of drug. It is obviously wiser to select a dose that is too small than one that is too large, for otherwise the pancytopenia may be extremely troublesome or fatal when it finally occurs.

BLEOMYCIN. Bleomycin[8, 85] is an antibiotic that is unique in its effects and its toxicity. It was originally isolated in Japan and is now available in the United States from the National Cancer Institute and Bristol Laboratories on an experimental basis.* Bleomycin is a DNA inhibitor that is specifically active against keratin-producing cells. It is therefore effective in a variety of squamous carcinomas that had hitherto been unresponsive to chemotherapy. This list includes squamous carcinoma of the cervix and carcinoma of the esophagus as well as carcinoma of the penis and vulva and other carcinomas of the skin. Two patients with unresectable carcinoma of the anus have recently been reported as apparently cured by a combination of bleomycin and CCNU. Bleomycin also has been used in combination with vinblastine at the M. D. Anderson Hospital in the chemotherapy of nonseminomatous metastatic testicular tumors. This combination apparently has produced a higher percentage of responses than was seen with previous forms of conventional chemotherapy.

Bleomycin has significant cutaneous toxicity in a high percentage of patients, causing dermatitis in many patients and eczema as well as edema in some patients. I had one patient who required a considerable amount of colloid and other intravenous fluids on an emergency basis to restore his fluid volume after the onset of bullous edema. Fever, chills, and pain from local injections occur as common side effects of bleomycin therapy, but do not limit therapy in most cases. Anaphylaxis occurs in 2% to 3% of patients and may be fatal. The most common limiting side effect is pulmonary toxicity, which occurs after a total of approximately 300 mg of the drug has been administered. Pulmonary changes begin with a mild cough and rales and progress on a dose-related basis to pulmonary fibrosis, which is variable from patient to patient but may be fatal. Bleomycin is administered in our clinic according to the protocol shown on p. 55.

ADRIAMYCIN. Adriamycin[93] is an aminoglycoside antibiotic that has a broad spectrum of activity not seen with any other cancer chemotherapeutic agent. It has been shown to be effective in drug-resistant lymphosarcoma as well as in a variety of soft tissue sarcomas and bone tumors. It is under investigation at the present time in the entire spectrum of solid tumors and appears to be achieving results in patients who are unresponsive to other therapy. The drug is expensive and is available in limited supply, since the only source is in Italy at the present time. Most patients will therefore require treatment with Adriamycin by a specialist in chemotherapy. It is important for the general surgeon and surgeons of various specialties to be aware of the important effect of this drug on bone tumors and a variety of urologic neoplasms, including carcinoma of the bladder and ureter, so that patients may be appropriately referred to major medical centers for chemotherapy with Adriamycin.

I have used the drug in cooperation with the Central Oncology Group, which utilizes a brief loading course followed by 1 to 2 doses a week on a continuing basis until a total dose of 450 mg/M^2 (approximately 900 mg total dose) has been given. The total dose is limited because of cardiac toxicity, which apparently occurs inevitably if the maximum permissible total dose is exceeded by

*Bleomycin has recently been released for commercial distribution as Blenoxane. The doses formerly referred to as "mgms" are now termed "units."

PROTOCOL: BLEOMYCIN (NSC 125066, "BLEO," BLM)*

MINIMUM SUGGESTED LABORATORY STUDIES

Observation	*Pretreatment*	*Weekly*
WBC	x	x
Differential	x	x
Hct	x	x
Platelets	x	x
BUN	x	x
Alkaline phosphatase	x	x
SGOT	x	x
Chest x-ray	x	x
Palpable lesion measurements	x	x

Bleomycin is available as lyophylized powder in 15 mg ampules that are reconstituted in 5 ml of water for injection.

DOSAGE AND ADMINISTRATION

Many dosages and intervals have been tested without demonstration of clear-cut superiority by any single method. Since the drug is usually given on an outpatient basis, the following plan is used for convenience:

> 15 mg twice a week for 1 week; then 30 mg twice a week for 3 more weeks (total dosage 210 mg); nothing given during 4-week observation period, then weekly doses, 30 mg, for 3 more weeks (total dosage 300 mg); given IM or by slow IV "push" injection.

Pulmonary fibrosis usually does not occur except when high cumulative doses have been administered (total of 300 mg), but any sign of dyspnea, interstitial pneumonia, or rales should be an indication to temporarily withhold therapy. If the pulmonary signs and symptoms do not subside, bleomycin therapy should be discontinued.

*Based on Blum, R. H., Carter, S. K., and Agre, K.: Cancer 31:903, 1973; and Magers, C. F., and Agre, K.: Clinical summary on bleomycin—second addendum to new drug application report, Syracuse, N. Y., 1972, Bristol Laboratories.

too great a margin. I have not personally observed cardiac toxicity, because my patients have either reached the maximum usual dose and have been switched to other therapy, or they have not shown responses and have been terminated from Adriamycin therapy before the maximum permissible dose has been reached. Adriamycin causes alopecia in virtually all patients as well as depression in the white count, which is usually preceded by stomatitis. For this reason the white count as well as the creatine phosphokinase level and the ECG are checked regularly during the period of drug administration. The total dose of Adriamycin is usually administered over a period of 2 to 3 months. Therefore patients with rapidly growing tumors are unlikely to have the opportunity to respond to Adriamycin.

COMBINATION CHEMOTHERAPY[22, 39]

Conventional and experimental chemotherapeutic agents are used in combination for a wide variety of tumors. Many of these combinations are of only investigational interest and will not be discussed in detail. However, some combinations have achieved a well-established role in chemotherapy, and guidelines for their use will be given here. It should be emphasized that most of the combinations have not been compared in a satisfactorily randomized fashion against single drugs in equivalent cases, so it is frequently uncertain whether the combination is clearly superior to single agent therapy. Nevertheless, on theoretic grounds combination chemotherapy appears superior to single agent chemotherapy in many situations because the combination provides a broad spectrum of agents with noncompetitive toxicity and with a variety of mechanisms of specific therapeutic activity.

"Triple therapy" for carcinoma of the testes was one of the first combinations tested.[2] It has never been adequately compared against single drug therapy, but triple therapy with actinomycin D, MTX, and an alkylating agent—usually chlorambucil—remains the standard chemotherapy for testicular tumors in many institutions. This form of therapy is toxic. It requires attention to detail and usually requires the continuous hospitalization of the patient. Therapy is given as follows:

Actinomycin D	0.5 mg/day × 5, repeated weekly × 3
MTX	5 mg/day × 21
Chlorambucil	10 mg/day × 21

The three-drug combination is then repeated when toxicity has sufficiently subsided.

Chemotherapy with this combination has been reported to produce responses in up to 40% of patients, half of whom show complete response, some for long enough periods of time to be considered "cured." This form of triple therapy is also used as an adjuvant after surgery and/or radiation therapy for patients with retroperitoneal node metastases of testicular tumors.

The "five-drug combination" for carcinoma of the breast was first described by Cooper[16] in 1970, and the usefulness of this combination has been confirmed by many other investigators up to the present time. Cooper reported responses in 90% of patients, but responses are now reported more commonly in the range of 50% to 60%.[63, 99] The five-drug combination has practical application because the patient can be seen on a weekly basis as an outpatient, receiving injections of 5FU, MTX, and vincristine according to the guidelines shown in the protocol on p. 57, and receiving prednisone and cyclophosphamide on a daily self-administered oral basis. A major drawback to the five-drug program is the difficulty in selecting other therapy for the patient who does not respond and for the patient who becomes resistant to the combination. Since several of the drugs that are most useful for carcinoma of the breast are included in this combination, and since the lifetime of a patient with metastatic carcinoma of the breast may be measured in many months to years, it is awkward to be faced with a patient who has already been treated with many of the best available drugs and is no longer responding. If the five-drug program actually "cured" some patients, it would obviously be worthwhile to use it intensively and for a prolonged period

PROTOCOL: FIVE-DRUG THERAPY FOR CARCINOMA OF BREAST*

LABORATORY STUDIES

Patients should have WBC and platelet count weekly; SMA 18 before therapy and at monthly intervals; and measurements of suitable tumor parameters at 1- to 4-week intervals.

DOSAGE AND ADMINISTRATION

5FU	500 mg IV	Weekly
MTX	25 mg IV	Weekly
Vincristine	1 mg IV	Weekly
Cyclophosphamide	100 mg PO daily with breakfast	
Prednisone	45 mg PO daily × 7, then	
	30 mg PO daily × 14, then	
	15 mg PO daily	

For WBC less than 4000, hold MTX and cyclophosphamide; for WBC less than 3000, hold MTX, cyclophosphamide, and vincristine; for WBC less than 2500, hold all drugs except prednisone; for loss of knee jerks, hold vincristine for 2 weeks and resume only if no weakness or painful neuritis appears; for stomatitis, hold MTX and 5FU; for hematuria, hold cyclophosphamide; for epigastric pain, hold MTX and prednisone. Cyclophosphamide will probably cause alopecia, and patient should be so informed.

This combination of drugs can be administered entirely on an outpatient basis and has been associated with less than 1% mortality vs 60% to 90% responses.

*Based on Cooper, R. G.: Proc. Am. Assoc. Cancer Res. **10**:15, 1969; and Ramirez, G.: Proc. Am. Assoc. Cancer Res. **14**:17, 1973.

of time. However, "cures" are not observed in chemotherapy for carcinoma of the breast, and it is probably more important to be able to utilize intelligent sequential chemotherapy for palliation rather than intensive combination therapy—except in patients who are desperately ill from painful or dangerous metastases when first seen. It should be noted that the five-drug combination has relatively little effect on patients with cerebral metastases; radiation therapy or nitrosourea derivatives should be utilized for these patients.

The COPP and MOPP[79]* programs for lymphosarcoma are now well-established combination chemotherapeutic regimens. The COPP program is explained in the protocol on p. 58. These programs are difficult to administer if the patient has had considerable prior chemotherapy, and drug doses must therefore be appropriately reduced. However, the COPP and MOPP programs appear to be appropriate for initial chemotherapy of the patient with reticulum cell sarcoma. They can be utilized by practitioners who are willing to observe closely for toxic side effects and manage their patients with the goal of palliation rather than

*Acronym formed from mechlorethamine (HN2), Oncovin (trade name for vincristine), procarbazine, and prednisone.

PROTOCOL: COPP THERAPY FOR LYMPHOSARCOMAS AND RETICULUM CELL SARCOMAS (10-DAY COURSES)*

Cyclophosphamide (Cytoxan)	10 mg/kg on days 1 and 8 of 10-day course
Vincristine (Oncovin)	0.04 mg/kg on days 1 and 8 of 10-day course
Procarbazine	2.5 mg/kg on days 1 through 10 of 10-day course
Prednisone	1 mg/kg on days 1 through 10, courses 1, 3, and 5 only

For initiation of therapy, five courses are used. The interval without treatment between courses is lengthened successively—2 weeks before the second course, 3 weeks before the third course, 4 weeks before the fourth course, and 5 weeks before the fifth course. Subsequent courses are given at 2-month intervals for 6 months and then 3-month intervals for 1 year.

*Modified from Hill, G. J., II: In Hill, G. J., II, editor: Outpatient surgery, Philadelphia, 1973, W. B. Saunders Co.

PROTOCOL: VCFM THERAPY FOR TESTICULAR CANCER*

MINIMUM REQUIRED LABORATORY STUDIES

Observation	*Pretreatment*	*During therapy*	*Weekly*
WBC	x	Days 1, 3, 5	x
Hct	x	Days 1, 3, 5	x
Differential	x		
Platelets	x	Days 1, 3, 5	x
Urinalysis	x		
BUN	x		x
SGOT	x		x
Alkaline phosphatase	x		x
Bilirubin (I & D)	x		x
Chest x-ray	x		x†
HCG (24 hr urine)	x		

DOSAGE AND ADMINISTRATION

Day 1

5FU	7.5 mk/kg IV
Cyclophosphamide	7.5 mg/kg IV
MTX	0.75 mg/kg IV
Vinblastine	0.05 mg/kg IV

Days 2 and 3

5FU	7.5 mg/kg IV

Day 4

5FU	7.5 mg/kg IV
Cyclophosphamide	7.5 mg/kg IV
MTX	0.75 mg/kg IV
Vinblastine	0.05 mg/kg IV

Day 5

5FU	7.5 mg/kg IV

Repeat course in 2 to 4 weeks as soon as WBC $>$ 4500 and platelet count $>$ 100,000.

*Based on Jacobs, E. M., Johnson, F. D., and Wood, D. A.: Cancer **19**:1697, 1966; Mendelson, D., and Serpick, A. A.: J. Urol. **103**:619, 1970; and Samuels, M. L., and Howe, C. D.: Cancer **25**:1009, 1970.

†If measurable lung lesions are being followed.

PROTOCOL: COMF THERAPY*

MINIMUM REQUIRED LABORATORY STUDIES

Observation	*Pretreatment*	*Weekly*	*Monthly*
WBC	x	x	
Hct	x	x	
Platelets	x	x	
Urinalysis	x		x
BUN	x		x
SGOT	x		x
Alkaline phosphatase	x		x
LDH	x		x
Bilirubin (I & D)	x		x
Chest x-ray	x		x†

DOSAGE AND ADMINISTRATION

Dosage is based on ideal or actual weight; whichever is lower determines the patient's dosage.

Cyclophosphamide	7.5 mg/kg given weekly IV; not to exceed 800 mg (usual dose 400 mg)
5FU	4 mg/kg given weekly IV; not to exceed 500 mg (usual dose 250 mg)
Vincristine	0.02 mg/kg given weekly IV; not to exceed 1.5 mg (usual dose 1.5 mg)
MTX	0.05 mg/kg taken daily PO; not to exceed 5 mg daily (usual dose 2.5 mg)

Discontinue if WBC is less than 3000 and platelet count is less than 75,000; discontinue MTX if patient developes stomatitis or diarrhea; discontinue vincristine if signs of peripheral neuropathy occur.

*Based on Costanzi, J. J., and Coltman, C. A., Jr.: Cancer **23**:589, 1969.
†If measurable lung lesions are being followed.

cure. Surgeons should be aware of the risk of sepsis that exists in their patients who have undergone staging procedures.[21, 98]

Several other combinations that have been described recently include Adriamycin and DTIC for sarcomas[43]; bleomycin and vinblastine (Velban)[113] and vinblastine (Velban), cyclophosphamide (Cytoxan), 5FU, and MTX (VCFM)[58] for testicular tumors (see protocol on p. 58); cyclophosphamide, vincristine (Oncovin), MTX, and 5FU (COMF)[17] (see protocol on p. 59), cyclophosphamide, vincristine, and 5FU (CONFU)[119] (see protocol on p. 60), and vincristine and cyclophosphamide for neuroblastoma[33]; 5FU and BCNU for adenocarcinoma of the gastrointestinal tract[75]; vincristine, actinomycin D, and cyclophosphamide (VAC)[24] for embryonal rhabdomyosarcoma in children; and BCG, isoniazid (INH), and MTX for squamous cancer of the head and neck.[23] All of these combinations are investigational at the present time.

PROTOCOL: CONFU THERAPY*

MINIMUM REQUIRED LABORATORY STUDIES

Observation	*Pretreatment*	*Weekly*	*Monthly*
WBC	x	x	
Hct	x	x	
Platelets	x	x	
Urinalysis	x		x
BUN	x		x
SGOT	x		x
Alkaline phosphatase	x		x
LDH	x		x
Bilirubin (I & D)	x		x
Chest x-ray	x		x†

DOSAGE AND ADMINISTRATION

Dosage is based on ideal or actual weight; whichever is lower determines the patient's dosage. The drugs are given weekly.

Cyclophosphamide	7.5 mg/kg given IV; not to exceed 800 mg (usual dose 400 mg)
5FU	4 mg/kg given IV; not to exceed 500 mg (usual dose 250 mg)
Vincristine	0.2 mg/kg given IV; not to exceed 1.5 mg (usual dose 1 mg)

Discontinue if WBC is less than 3000 and platelet count is less than 75,000; discontinue vincristine if signs of peripheral neuropathy occur.

*Based on Tucker, W. G., et al.: Cancer Chemother. Rep. **52**:593, 1968.
†If measurable lung lesions are being followed.

METHODS

Therapy with antineoplastic agents is usually given orally or intravenously. Some of the agents, particularly the hormones, can be given intramuscularly at home or by a nurse rather than requiring a doctor's supervision, but most of the cytotoxic drugs are not available for intramuscular injection.

A wide variety of other routes of drug administration are under investigation, most of which are more time-consuming, more hazardous, or more expensive than conventional methods. I will review here the current attitudes toward the special methods that have recently been described or are under continuing investigation.

Perfusion

Perfusion of the extremities continues to receive interest and support, but this method has never received wide acceptance by the medical and surgical community. Perfusion utilizes the complete isolation of the arterial and venous blood flow from an area; during the period of perfusion the blood is circulated through a pump oxygenator. The use of perfusion appears mainly to be limited to the treatment of sarcomas and melanomas of the arm and leg located far enough distal to the axilla and groin to permit isolation perfusion.

Isolated limb perfusions are performed to deliver a high concentration of chemotherapeutic agent to the localized area. The most commonly used agent at present is melphalan (phenylalanine mustard), which is used in a dose of 1 mg/kg. The drug can be obtained on special request from the manufacturer.* The parenteral form of melphalan is not available on a commercial basis. The dose of 1 mg/kg is close to or just beyond the maximum safe single dose for intravenous administration.

If melphalan is not selected because of another preference by the investigator or because of difficulty in obtaining the drug on short notice, actinomycin D, HN2, or thio-tepa can be substituted. The dose of any of these drugs should be no greater than the largest single dose administered systemically. This would be, for example, 0.4 mg/kg for HN2; 5 mg for actinomycin D; and 60 mg for thio-tepa. The dose should be lowered if the blood count has been reduced by prior chemotherapy, radiation therapy, or myelophthistic changes or in patients of lower than normal weight.

Recent investigations have demonstrated that the beneficial effect of perfusion may result to some extent from the hyperthermia utilized; it appears that the maximum tolerable, safe temperature should be used for perfusion with intramuscular thermocouple recordings performed continuously during the procedure.

We have found suitable indications for perfusion in only three patients out of 700 referred for cancer chemotherapy, and obvious benefit was not achieved in any of these patients. The addition of perfusion to groin dissection and wide excision or amputation adds to the morbidity of the primary operation. On the other hand, the continued reports of success wth low morbidity and essentially zero mortality from Creech and Krementz[18] at Tulane University indicate that experience with the procedure is a significant factor in achieving results.

Infusion

Regional infusion therapy[25, 114] refers to the administration of a chemotherapeutic agent into the artery supplying a tumor or tumor-bearing organ (in the case of the liver, either the hepatic artery or the portal vein). Infusion therapy has been simplified in recent years by improvement in percutaneous arterial catheter placement. The radiologic techniques utilized in assessing catheter position have made long-term infusions more satisfactory. The procedure is still a tedious one for both the patient and the physician, and infusion therapy has not achieved wide popularity. I believe that if hepatic artery infusion is performed it should be done after surgical convalescence rather than in the immediate postoperative period. I therefore do not routinely place a catheter in the gastroduodenal artery, as has been recommended by others, even when a tumor is discovered that will presumably later be treated by infusion therapy. I prefer to allow the patient to recover for 7 to 10 days after major abdominal surgery and then request arteriographic studies and arterial catheter placement by the radiology department. Collaboration with the radiologist ensures continuing follow-up by specialists in angiography; this is essential in order to maintain good catheter position.

*Burroughs Wellcome Co., Research Triangle Park, N. C.

I prefer the brachial rather than the femoral artery in most cases because the patient can be ambulated and because the dangerous consequences of peripheral emboli are apparently less common in the arm than in the leg. The Watkins infusion apparatus* is available for long-term infusions, but I prefer the less expensive, disposable pneumatic plastic bag and tubing supplied by the Abbott and Fenwal companies.† The main indications for infusion therapy at the present time are hepatic artery infusions for metastases to the liver and external carotid infusions for head and neck cancer. For hepatic artery infusions I utilize the method described by Wirtanen et al.[3, 127] at the University of Wisconsin. This therapy utilizes 5FU in a dose of 30 mg/kg daily for 4 days followed by 15 mg/kg for 11 more days. 5FU hepatic arterial infusion is toxic and often requires interruption because of depression of the white count. The patient should be monitored daily, checking weight and performing liver function tests, white count, and platelet count. Any significant, sudden change in any of these parameters would be an indication for switching from 5FU to an infusion of glucose and water. I ordinarily administer approximately 5000 units of heparin in each 24 hr period to maintain catheter patency and to reduce the risk of microemboli.

Infusion therapy can be given for head and neck tumors and for other tumors that are sensitive to MTX, using doses that would ordinarily not be tolerated but that can be made tolerable by the simultaneous oral or parenteral administration of citrovorum factor.[6] I have had no personal experience with this type of therapy, although it is logical and has been highly recommended by those who practice it.

Short-term high-dose combination infusion chemotherapy for head and neck tumors has been described by Cruz and Aust,[20a] and I have found their method of administration of 5FU, vinblastine, and MTX to be acceptable. It has the advantage of allowing drugs with a variety of actions to be administered and also achieves therapeutic activity in a short period of time, so that the catheter can be removed before it is accidentally dislodged or the small artery becomes occluded. The therapy utilizes the following regimen:

5FU	15 mg/kg/day	To moderate local or systemic toxicity or a maximum of 10 days
MTX	5 mg/day	
Vinblastine	0.02 mg/kg/day	

The white count and platelet count are measured daily, and therapy is interrupted when the white count is less than 3500 or the platelet count is less than 150,000.

Hyperalimentation

Hyperalimentation[82] has been discussed informally by many investigators as a possible means for maintaining good nutritional balance when cytotoxic drugs that reduce appetite are being administered. This would appear to be particularly appropriate when hepatic artery infusion is being carried out or other moderately

*United States Catheter and Instrument Corp., Glens Falls, N. Y.

†Abbott Scientific Products Co., Abbott Laboratories, South Pasadena, Calif.; Fenwal Laboratories, Division of Travenol Laboratories, Inc., Morton Grove, Ill.

long but limited courses of parenteral chemotherapy are being given, providing the risk of sepsis is reduced by careful management.[41] I have had personal experience with this method in one patient in whom obvious benefit was seen. The patient's condition appeared terminal because of recurrent carcinoma of the colon associated with abdominal fistulas. She was vigorously managed with hyperalimentation; most of her fistulas healed, and she gained 20 pounds in weight. At this point parenteral 5FU therapy was begun, and she was transferred to outpatient status. Although her tumor never showed a complete response to 5FU and she eventually died as a result of progression of the neoplasm several months later, the beneficial effect of hyperalimentation in preparing her for chemotherapy was clearly apparent.

Combined radiation and chemotherapy

Radiation therapy and chemotherapy[27, 49, 90] are under investigation as a combined method of therapy, but the most effective means of delivering these two modalities simultaneously is still uncertain. 5FU is the drug most commonly utilized. In patients with recurrent carcinoma of the colon it appears to be necessary to reduce the dose of 5FU by approximately 50% when a full course of cobalt therapy is being administered simultaneously. Cell kinetic studies in laboratory animals indicate that significant potentiation of effect of these two modalities can occur when proper synchronization of chemotherapy and radiation therapy is achieved. It is difficult, however, to utilize cell kinetic studies in humans to select the dose and interval of therapy.[47] Therefore this combined modality of therapy remains in an empirical stage at the present time.

Intraluminal therapy

Intraluminal therapy with 5FU has been utilized intermittently for more than 15 years. The oral route is not approved as far as the manufacturer or the FDA is concerned, but it is in wide enough use to warrant some comment about it. The oral form of 5FU was tested when the drug was first released for investigational use, but this method was discarded because its effect was not as predictable as the effect achieved when 5FU was given intravenously. Oral 5FU has been restudied within the past 3 years and good results have been obtained,[76] particularly in patients with hepatic metastases of adenocarcinomas of the intestinal tract. A randomized study confirmed the benefit of oral 5FU in comparison with conventional intravenous 5FU.[5] Because of these reports, I administered 5FU by the oral route in preference to the intravenous route for approximately 9 months. However, I was not sufficiently impressed with the results to continue this therapy as the preferred method. I noted that several patients were maintained in remission, which had been induced by intravenous 5FU. However, I induced no new remissions with oral 5FU during the 9-month period despite attempts with more than a dozen patients who had objectively evaluable adenocarcinomas of the gastrointestinal tract and breast. 5FU appears to be tolerated in larger doses orally than intravenously. The toxic side effects are essentially the same, however, when toxicity is reached. The oral route does make it possible to utilize schedules that are not available for the intravenous route except for patients who are continually hospitalized. For instance, the drug can be given on a daily basis or in multiple small daily doses,[61] measured by eyedropper or

teaspoon. Unfortunately I have seen no particular benefit from any of these different schedules, although no specific study has been designed and performed to test each oral dosage schedule. At the present time the Central Oncology Group is evaluating the oral route in comparison with three intravenous regimens in a randomized study. The results of the study are not yet available for analysis.

Intraluminal 5FU has been utilized by Rousselot et al.[103] at St. Vincent's Hospital in New York at the time of elective colon resection for carcinoma. The published results are encouraging, but the method has not been widely accepted for reasons that are not clear.

Topical therapy

Topical 5FU therapy has been studied extensively on an experimental basis by Litwin[75] and Klein[68] and has achieved significant benefit for patients with basal and squamous cell cancers. Surgical or radiologic therapy would have been disfiguring in many of these cases. Litwin has observed excellent results with 5% or 10% 5FU ointment and cream. This therapy remains investigational, and at the present time 5FU cream is available only for treatment of dermatosis.

Intralesional therapy

Intralesional therapy with cancer chemotherapeutic agents has been utilized on a somewhat informal investigational basis by cancer chemotherapists for many years. Patients with melanoma or similar disorders appear to be ideal candidates to have a small dose of different therapeutic agents injected into each of several melanomas as in vivo human models for biologic effectiveness. In practice, however, this method has not really been particularly useful. Recently Klein[67] at Roswell Park has utilized intralesional injection or topical application of various agents that probably act through an immunologic mechanism rather than specific local toxicity.

The chemosurgery described by Mohs[91] continues to be useful in the hands of those who are experienced with this technique, but it has not achieved wide acceptance.

It is obvious that intralesional therapy with strong destructive agents or immunologic adjuvants has theoretic application for patients who have well-localized but unresectable disease. Presumably better use will be made of these methods in the future.

Intralesional immunotherapy is described on p. 65.

Varying drug administration

Variations in cycles and intervals of drug administration are under investigation in strict protocols and in somewhat looser individual investigations throughout the country. The usual diurnal and solar periods are convenient periods for drug doses to be administered, but do not have any necessary relationship to the biologic activity of the tumor or to the patient's recovery from toxicity. Therefore, although we usually administer drugs at 8, 12, or 24 hr intervals, or on a weekly basis, or in monthly courses, it is more appropriate for the patient to be assessed for toxicity and effectiveness on an individual basis. Drugs must not be repeated in identical doses and at identical periods simply for the record, but an ap-

propriate toxic/therapeutic effect should be sought. Bone marrow reserve can be quantitated by the Piromen test[69] in patients who are expected to have decreased reserve because of prior irradiation therapy, chemotherapy, or marrow involvement by the tumor. High-dose continuous schedules are now utilized for cytosine arabinoside in leukemia, and similar methods are being explored for the administration of the antimetabolite 5FU. A 48 hr infusion has been standardized for a safe dose of 30 mg/kg daily for 48 hr,[54] repeated at 2-week intervals. Other such schedules will undoubtedly evolve in the near future.

IMMUNOLOGIC THERAPY

Immunologic therapy is achieving considerable interest, but the safety and indications for this type of therapy are still not clear in practice. BCG (bacillus Calmette-Guerin)[45] is the most widely used of the immunologic methods because of its ready availability as a tuberculosis prophylactic agent. It appears to be of most significant effect in patients with well-localized intradermal recurrent melanoma,[122] in which intralesional injections of 0.1 to 0.5 ml of BCG at 1- to 4-week intervals have produced complete remission in some patients who have previously failed to respond to surgery, radiation therapy, and chemotherapy. Several of these patients have been in complete remission[92, 97] for extended periods of time and may be considered cured. The incidence of this type of response and the total number of these patients successfully treated are unknown at the present time; it is probable that this information will be difficult to assess. It is also probable that many severe reactions from BCG have not been recorded and that the potential harm from this therapy may be as great as its potential benefit.[51, 87] BCG causes fever and chills in most patients after intralesional injections,[4, 112] and progressive BCG disease has been demonstrated in a few patients. The BCG organism usually responds to antitubercular therapy, but at least two deaths have recently been described in which patients were found to have both disseminated BCG organisms and disseminated tumor present at postmortem examination.

Despite the potentially ominous side effects of BCG administration, the interest in this form of therapy still continues because of the well-documented good results that have occurred in some patients. BCG produces increased morbidity in patients who have positive tuberculin skin tests or especially in patients who have previously had active tuberculosis. BCG should be used with great caution in such patients, and many investigators decline to administer it to patients who have previously had tuberculosis. In any case, the tuberculin skin test should be performed before and during courses of BCG administration. The Tice* and Glaxo† strains of BCG can be obtained for use in antituberculous therapy, and it is these strains of BCG that appear to be most commonly used in the clinical trials of cancer immunotherapy at present in the United States. It should be emphasized that this therapy should be performed only with the consent of the institutional human research committee and the informed consent of the patient, for there is no presently approved method, dose, route, or indication for BCG therapy of cancer at the present time.

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*Research Foundation, Chicago, Ill.
†Eli Lilly & Co., Indianapolis, Ind.

Other forms of immunologic therapy under investigation include tumor vaccine, cross-exchange transfusions of sensitized plasma and leukocytes, Coley's toxin, heterologous cells and serum, and neuraminidase-treated tumor preparations.[110] All of this therapy is strictly investigational and has no role in general clinical practice at the present time. An interesting hypothesis has recently been advanced suggesting that the mechanism of action of some of the chemotherapeutic drugs used in the treatment of cancer may be in their effects on the immunologic systems of the patients.[105]

CURRENT CONCEPTS IN THERAPY OF SPECIFIC TUMORS

Carcinoma of lung

Carcinomas of the lung are notoriously resistant to chemotherapy. Oat cell cancer appears to be the most sensitive,[13] and certainly any patient with oat cell carcinoma should be considered a potential candidate for chemotherapy and radiation therapy rather than surgery, since the surgical curability of this tumor is essentially nil.[44, 125] High-dose cyclophosphamide therapy is probably the chemotherapeutic treatment of choice for oat cell carcinoma (10 to 15 mg/kg intravenously weekly [Fig. 3-1]), but the primary tumor area should ideally be radiated as well. The results are apparently improved when MTX and vincristine have been added to the cyclophosphamide, although there is no clear indication that a substantial cure rate will be achieved even by the most intensive therapy with cyclophosphamide, MTX, and vincristine. Several months of good palliation can be achieved, however. Cyclophosphamide would be a reasonable drug to use in most of the squamous carcinomas and adenocarcinomas of the lung, since these tumors frequently have poorly differentiated elements and since no other drug is clearly preferable to cyclophosphamide. However, for well-localized, well-differentiated squamous carcinomas of the lung, 5FU and MTX would probably be preferable to cyclophosphamide on theoretic grounds, and 5FU would theoretically be the best treatment for well-localized, well-differentiated surgically incurable adenocarcinoma of the lung. I hasten to emphasize that I have never, however, seen benefit in such patients from 5FU and MTX, and I inevitably utilize new investigational agents such as CCNU[118] because of the poor record of conventional drug use in such patients.

Analysis of 221 consecutive cases of carcinoma of the lung treated at the University of Colorado between 1961 and 1967 revealed that radiation therapy and chemotherapy were associated with as high a percentage of survival at each successive time interval following diagnosis as was treatment by surgery alone. Obviously patients with well-localized peripheral tumors must be treated by surgery if resection will be tolerated by the patient. On the other hand, radical surgery for patients with extensive, centrally located lesions is less well tolerated and has no statistical benefit over the results achieved with radiation therapy and chemotherapy. Of the 6% of the 221 patients achieving long-term (greater than 3 years) survival, half had been treated only by surgery and the other half treated by radiation and chemotherapy for apparently "incurable" disease.

The use of biopsy of nonpalpable scalene nodes[10] has reduced the incidence of operations that result only in exploratory thoracotomy and biopsy, and preoperative evaluation by mediastinoscopy has also increased the curability rate

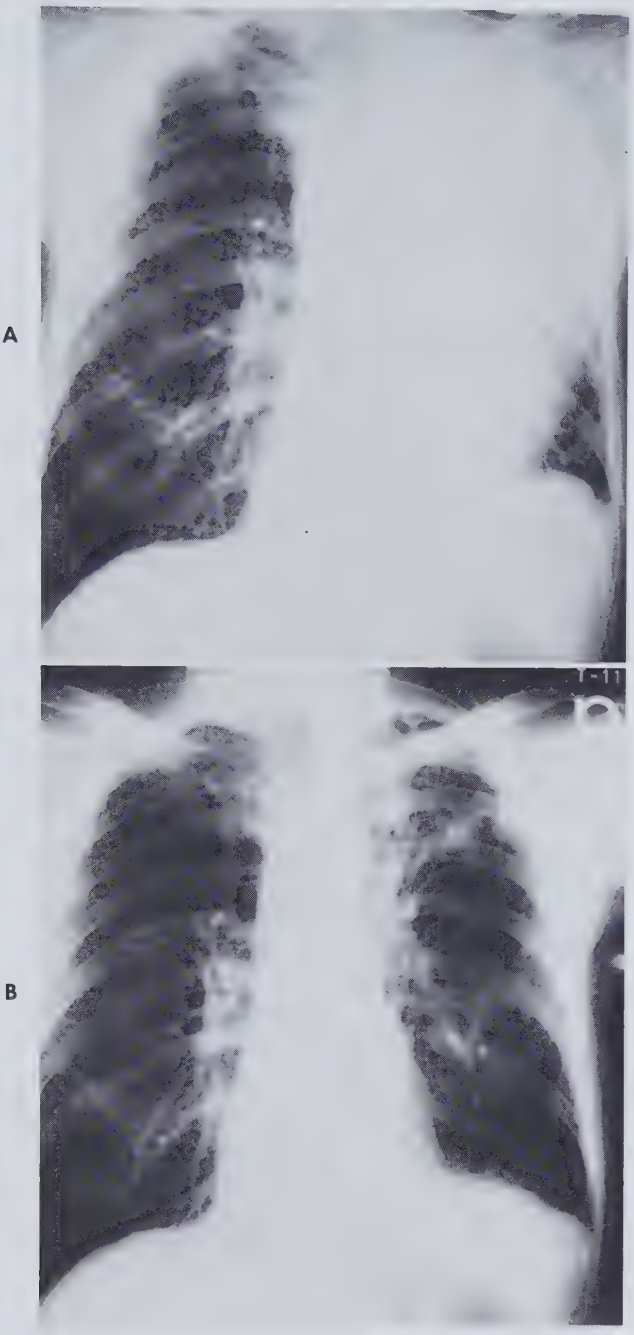

Fig. 3-1. Carcinoma of lung. This 70-year-old man was hospitalized for back pain caused by thoracic spine metastasis from poorly differentiated tumor. Diagnosis made by incisional biopsy of right scalene node. **A,** Pretreatment x-ray film. **B,** Chest x-ray film taken after 3 months of treatment with intravenous cyclophosphamide, 10 mg/kg weekly, as outpatient and localized ^{60}Co to involved vertebrae. Complete resolution of nodal metastases occurred and considerable improvement was noted on chest x-ray film. Patient was free of pain and symptoms for 9 months and then rapid progression of tumor occurred.

achieved by resection.[95] The patients who are deemed incurable because of extensive mediastinal disease or spread to the contralateral mediastinal nodes are the patients treated immediately with radiation therapy, followed by chemotherapy when the toxicity from radiation therapy has subsided. If the patient is unable or unwilling to tolerate radiation therapy, I would immediately begin cyclophosphamide therapy. Radiation therapy is clearly better than chemotherapy for the management of hemoptysis and pain due to carcinoma of the lung, but pleural effusion is usually better treated with HN2 through a chest tube, as described previously.

Recent publications suggest that postoperative empyema[104] and an advanced parental age[111] correlate favorably with increased survival in lung cancer, but clear-cut demonstration of prolongation of life from chemotherapy has not been achieved.

Adenocarcinoma of gastrointestinal tract

Adenocarcinoma of the gastrointestinal tract can be considered a general problem in cancer chemotherapy, for the differences in response in the various gastrointestinal carcinomas are probably more the result of individual growth rates and variation in metastatic patterns of spread than significant variations in response to chemotherapeutic agents. 5FU is essentially the only drug that has any major effect against adenocarcinomas of the gastrointestinal tract. This includes adenocarcinoma of the stomach, pancreas, small intestine, bile ducts, colon, and rectum as well as hepatomas in adults. Other types of gastrointestinal neoplasms obviously have different responses to therapy, as in carcinoma of the esophagus (which is essentially unresponsive to conventional drugs, but possibly responsive to bleomycin in some cases), reticulum cell sarcomas and lymphomas of the stomach (which are treated as lymphomas and reticulum cell sarcomas of other parts of the body—with resection, irradiation, and chemotherapy as determined by the location and extent of disease), and carcinomas of the oral cavity and anus, which present special problems. Carcinoma of the oral cavity is treated as are other squamous carcinomas of the head and neck (see discussion of head and neck cancers on p. 80). Carcinoma of the anus is usually squamous or cloacagenic (sometimes called "undifferentiated"). These tumors do not respond to 5FU, but a few have responded to bleomycin or bleomycin and CCNU. Two long-term remissions have been recorded in squamous carcinoma of the anus with the latter combination of drugs by Fletcher[34a, 74a] of the University of Oregon; for this reason the combination of bleomycin and CCNU remains under investigational study for squamous carcinoma of the anus. I have never seen a response in cloacagenic carcinomas using any of a variety of conventional or experimental drugs, and I ordinarily turn to new agents for chemotherapy of such tumors.

Adenocarcinomas of the colon, stomach, and pancreas represent the most common gastrointestinal tract carcinomas encountered. These respond to 5FU in approximately 15% to 30% of evaluable cases. Unfortunately less than half of the patients with recurrent or metastatic colorectal cancer have evaluable lesions, and the percentage is even smaller in carcinomas of the stomach and pancreas.

It is unusual to encounter a patient with an objectively evaluable tumor mass of metastatic carcinoma of the pancreas. Responses, therefore, are usually judged

as either failures or dramatic cures when the patient either dies of progressive jaundice, often with considerable pain and inanition or has a clear-cut remission of jaundice due solely to administration of chemotherapy. I have personally seen 4 patients out of 30 treated with objective regression of extensive carcinoma of the pancreas. All of the patients subsequently relapsed and died, but the results were objectively evaluable during the period of remission. Three of these patients underwent laparotomy for various reasons, and the regression of the primary tumor and/or extensive peritoneal implants was thereby documented. In the fourth patient, large pulmonary metastases regressed completely during therapy. Therapy in three of these patients was with 5FU alone, and the fourth patient was treated with a combination of 5FU and the investigational drugs tubercidin and Streptozotocin. A recent report from Children's Hospital and Peter Bent Brigham Hospital, both in Boston, describes a continuing complete remission in a patient with carcinoma of the pancreas treated with 5FU and BCNU.[77] Carcinoma of the pancreas occurs at the most rapidly increasing rate of any carcinoma in the United States with the possible exception of carcinoma of the lung. Obviously more effort will be directed to evolve better programs of evaluation and chemotherapeutic control for this tumor, since it is usually incurable when first detected, and the optimum surgical management of the primary tumor is still debated.[19, 35]

Carcinoma of the stomach is one of the most difficult tumors to evaluate because the rate of growth of the tumor is extremely variable. Some patients have lived for several years after a resection in which the tumor was incompletely removed or present at the margin of the resected specimen. I have, however, seen several cases in which chemotherapy with 5FU appeared to produce benefit, and observed 2 out of approximately 30 patients treated in which objective benefit was confirmed by partial regression of tumor masses. One of these patients was treated with the investigational drug tubercidin, and the other was treated with 5FU. The most impressive benefit, however, occurred in patients who had palliative resections or bypass procedures and who received 5FU postoperatively. Although reexploration was not done in any case to confirm regression of the tumor, three of the patients experienced perfect health for more than a year before progression and symptoms occurred again. In one case a patient over age 80 years underwent palliative gastrojejunostomy with an anastomosis performed through the tumor. Complete obstruction was present preoperatively; the situation was only slightly better postoperatively, but the patient resumed normal alimentation when 5FU therapy was started. He continued on outpatient therapy, having regained his normal weight, and was asymptomatic for more than 12 months, at which time supraclavicular metastases and a recurrence of gastric symptoms were noted.

This type of 5FU therapy utilizes weekly outpatient doses of 500 mg intravenously, which is safe and has virtually no symptomatic side effects. Therapy with 5FU appears to be indicated in such patients even if responses are achieved in only a small percentage.

Incurable adenocarcinoma of the colon and rectum is best treated with 5FU in conjunction with palliative surgical procedures and radiation therapy directed at painful or bleeding lesions. It is uncertain whether patients should be treated with 5FU when metastases are first documented or only after the patient is

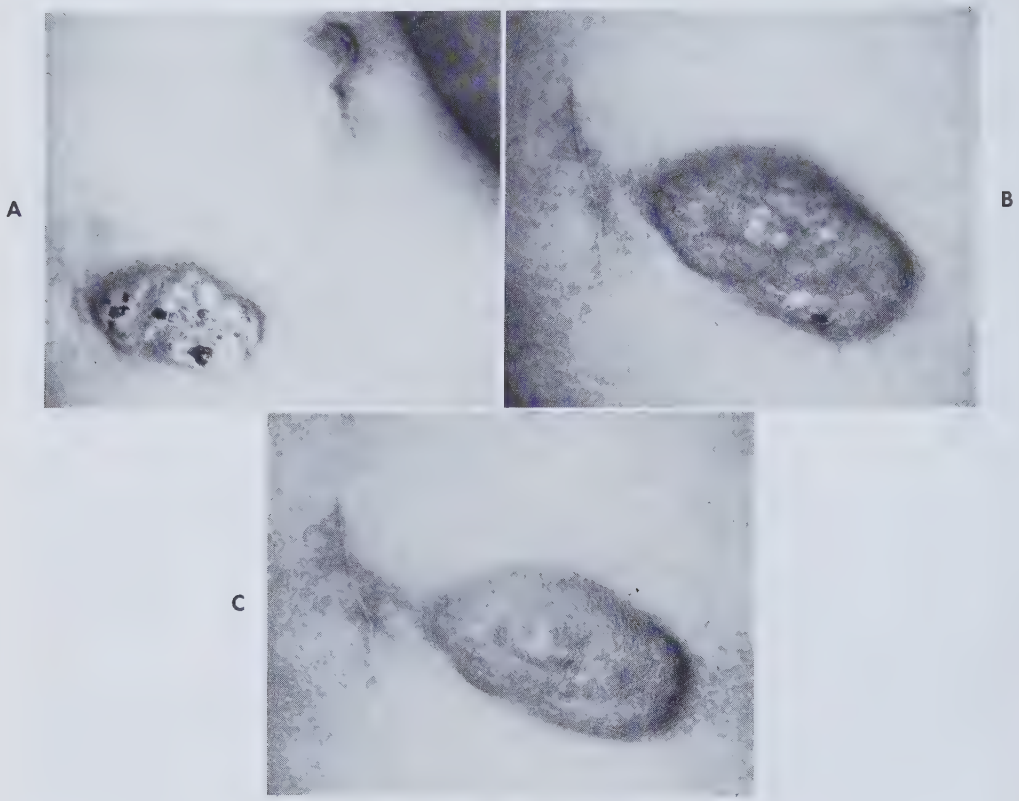

Fig. 3-2. Adenocarcinoma of cecum metastatic to skin and subcutaneous tissue of right flank. A large painful ulcerated mass recurred in right lateral abdominal wall and spread to axilla in this 60-year-old woman. **A,** Pretreatment view of ulcerated surface of metastasis adjacent to right flank drain site and metastasis in right axilla. **B,** Closeup view of right flank lesion 7 days after a 5-day "loading course" of 5FU, 500 mg/day. Ulceration is healing, subcutaneous mass is regressing, and pain is decreasing. **C,** Same lesion 28 days later, after four weekly 500 mg injections of 5FU. Ulceration is gone, no pain is present, and no deep mass is palpable. Patient subsequently developed progressive, fatal cerebral metastasis while extracranial tumor metastasis remained under control.

symptomatic and/or evaluable.[62] It is my conviction that 5FU can be administered safely as long as the guidelines described on p. 44 are followed, and it is therefore reasonable to treat patients either with a poor prognosis (Dukes' C)[26] or when well-documented incurability is present. On the other hand, it is not mandatory to treat such patients immediately, and the pros and cons of immediate treatment should be discussed with either the patient or a member of the family before it is instituted. The discussion should include a definite statement that no conventional drugs are likely to be beneficial when progression occurs after 5FU therapy has previously been given. A possible exception to this is the effect of 5FU infusion on hepatic metastases, which is occasionally beneficial even in patients who have previously received systemic 5FU.

At present I am engaged with the Central Oncology Group and the National

Cancer Institute in evaluating the relative merits of immediate chemotherapy in patients with a poor prognosis or incurable carcinoma of the colon as compared with the benefits of therapy when objective or symptomatic disease is present. This study involves randomization based on the parameters of location, symptoms, pathology, sex, and age of the patient. Half of the patients receive immediate 5FU therapy while the others receive 5FU only when progression is observed. The study is designed mainly to assess the duration of the interval free of progression and symptoms; survival is also assessed as a corollary of the study. Although the majority of patients with metastatic carcinoma of the colon are not evaluable until advanced disease is present, often with huge pelvic masses or large hepatic masses and jaundice, I have had sufficient opportunity to treat patients with pulmonary or superficial abdominal masses to conclude that 5FU can produce symptomatic and objective benefit in approximately 30% of objectively evaluable patients (Fig. 3-2). My previous report[53, 56] that 44% of patients with metastatic carcinoma of the colon and rectum responded to 5FU included an assessment of my patients with hepatic artery infusions, who responded in 80% of cases. The overall response rate from intravenous therapy is therefore lower than 44%, although I have not seen responses as infrequently as was reported by Ansfield (17%) at the University of Wisconsin.[1]

Hepatoma

Patients with primary carcinomas of the liver fall into essentially the following four categories: (1) The patient with cirrhosis and multicentric hepatoma is ordinarily so ill with advanced cirrhosis and/or multiple aspects of liver failure that no significant benefit is anticipated, and I have not seen any such patients helped by chemotherapy. (2) Primary bile duct carcinoma (cholangiocarcinoma) is a rare tumor that is usually slow growing and occasionally responds to 5FU therapy (see discussion of extrahepatic biliary tract adenocarcinomas on p. 72). (3) Children with embryonal hepatomas or some of the rarer forms of hepatoma are ordinarily treated by pediatric oncologists and will not be discussed here. (4) Otherwise healthy patients with solitary or multicentric hepatocellular adenocarcinomas are being seen more commonly in recent years as a result of increased surgical interest in this condition and the availability of liver scans and arteriograms to evaluate puzzling epigastric masses. I have seen several of these patients who have had large hepatomas that were either excised completely or underwent palliative resection, and in whom the question of chemotherapy was then raised. It is obvious that the mortality is variable, and up to 50% of such patients may be cured by surgical resection alone. However, in many cases the tumor is unresectable, muticentric, or already metastatic beyond the liver when first seen. In my experience with approximately 10 such patients I saw two who obviously benefited from therapy, although in neither case was the result necessarily due solely to 5FU. In one case the patient had a large primary hepatoma with metastases to the lymph nodes of the porta hepatis. A hepatic artery catheter was inserted and 5FU was infused. The hepatic artery became thrombosed in the course of this infusion. The right upper quadrant mass receded and never increased again in size. The patient underwent a second arterial infusion (celiac) approximately 4 months later, at which time she had an abdominal wall metastasis that receded during the infusion therapy—apparently due to "spill-

over" of 5FU into the systemic circulation. The patient did not develop hepatic failure even when the tumor subsequently metastasized throughout the body. The majority of the effect on the primary tumor may have occurred simply as a result of occlusion of the nutrient hepatic artery, but it was also apparent that the tumor was responsive to 5FU.

The second case involved a patient with spontaneous rupture of a hepatoma that occupied all of the right and part of the left lobe. The tumor and the adjacent liver tissue were evacuated in a palliative procedure, and the patient was treated with 5FU postoperatively. A liver scan 2 years later appeared essentially normal, and she remained well. 5FU therapy was stopped and she continues to remain well at the present time. Whether the tumor simply had a favorable biologic activity or whether 5FU played a significant role in this case is uncertain, but 5FU was clearly well tolerated and of no obvious harm to the patient.

Extrahepatic biliary tract adenocarcinoma

Carcinomas of the gallbladder and bile ducts are encountered occasionally and are usually fatal, although the length of survival is extremely variable, especially for bile duct cancers. Carcinomas of the extrahepatic bile ducts are often very slow growing, and the patient can often be well palliated by intubation of the ducts through the tumor or by a hepaticojejunostomy as described by Longmire. Such patients have often been concomitantly treated with 5FU by systemic or intra-arterial routes, and the results are difficult to evaluate. One of my best results in eight patients with carcinoma of the gallbladder or bile ducts was with a patient having extensive carcinoma located in this area. It appeared to arise in the gallbladder but may have actually been a common hepatic duct cancer. A T-tube was put in place during the operation, lying through the tumor, and the patient was started on 5FU postoperatively. The tube was removed by the patient approximately 3 months later, and 5FU therapy was continued with no evidence of disease for approximately 1½ years. At this time ascites developed and the patient was treated with COMF (see protocol for COMF therapy on p. 59). The ascites regressed and good benefit was achieved for another 6 months. When ascites again recurred, intraperitoneal HN2 was utilized, along with frequent paracentesis. The HN2 therapy also appeared to be beneficial, although this was difficult to assess quantitatively. After another 6 months of diminishing results, the patient died, and autopsy revealed that virtually all of the tumor in the abdomen was in the form of metasases to the ovary. The area of the liver and bile duct had only a small amount of tumor. This case illustrates the benefit of 5FU, which is documented in occasional sporadic reports in the literature. 5FU is clearly the drug of choice in patients with carcinoma of the gallbladder or bile ducts.

Carcinoid tumors

Carcinoid tumors are occasionally encountered as problems in metastatic cancer. The problems are mainly a result of the symptoms and physical changes produced by the hormones secreted by hepatic metastases rather than of widespread metastases or tissue invasion. The hormones secreted by carcinoid tumors include serotonin, 5-hydroxytryptophan, and bradykinin. The symptoms produced are difficult to treat, but may be palliated by careful management.[50] The most

serious problem in these patients is usually diarrhea, which can be managed reasonably well with Periactin. Retroperitoneal fibrosis in the carcinoid patient may cause bowel or ureteral obstruction and ascites. It is virtually impossible to control this type of retroperitoneal fibrosis with present therapeutic methods. Hepatic arterial infusion of chemotherapeutic agents and palliative resection of metastases have been reported to be helpful. 5FU is probably the most reasonable drug to use, but corticosteroids, diuretics, phenothiazines, and management of hyperperistalsis will also be of concern to the physician in treating such patients. The cutaneous "flushing" episodes are problems in ambulatory outpatients, who are embarrassed by the episodes, but no therapy is likely to control these symptoms without unacceptable side effects. Asthmatic attacks and bradycardia or hypotension are rare except in the presence of advanced, unresponsive disease. Psychiatric manifestations of the carcinoid syndrome are frequently very troublesome and may require confinement of the patient long before the tumor has caused cachexia. Vitamin supplements are given to counteract the niacin deficiency caused by abnormal tryptophan metabolism, and chlorpromazine is frequently useful, probably because of its alpha receptor blocking activity and its tranquilizing effects. I have seen one objective long-term response associated with cyclophosphamide, in which the urinary excretion of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) returned to normal for 1 year following prior elevation of two to three times the normal range. I have not been convinced of any consistent objective benefit in any of the other six patients with carcinoid tumors whom I have treated, although several appeared to show temporary benefit from 5FU, at least with respect to their episodes of cutaneous flushing.

Adenocarcinoma of breast

Chemotherapy appears to be achieving a somewhat greater role in the management of patients with carcinoma of the breast during the last few years. The safety and simplicity of hormone therapy has to some extent impeded the utilization of effective chemotherapy, because frequently patients were referred to oncologists for systemic therapy only after far-advanced disease was present, often with cerebral metastases or myelophthistic disease. The combination of five drugs[16] described previously has awakened interest in chemotherapy for carcinoma of the breast, but has made the problem somewhat more complicated because many patients now receive five drugs initially, and the problem of selection of other agents is obviously more complicated subsequently.[40]

I approach treatment of the patient with metastatic carcinoma of the breast with an assessment of her menopausal status, the location of obvious and suspected metastases, and the rapidity of progression of the tumor. Chemotherapy does not appear to play a significant role in therapy of primary carcinoma of the breast, and its use is therefore restricted to the treatment of patients with metastases, except for the investigational surgical adjuvant studies currently underway. Even the best method for therapy of the primary tumor is now being reexamined.[20, 46]

The premenopausal patient with recurrent or metastatic cancer should eventually receive an oophorectomy. If the first recurrence is small and at a late interval after the primary treatment, therapy for the metastasis may be simply reresection or local radiation, and oophorectomy may be deferred until a later time.

If, however, the recurrence or metastasis is large and rapidly progressing, oophorectomy should be done promptly. In any case, the effect of oophorectomy should be evaluated for at least 4 weeks with objective records made by photography or measurement to determine whether or not oophorectomy was beneficial. If oophorectomy is performed immediately after the diagnostic excision of the only metastasis that is present, it will be impossible to assess the benefit of the ablative procedure. It then is more difficult to decide whether to offer adrenalectomy, hormone therapy, or chemotherapy subsequently.

The premenopausal woman who responds to oophorectomy or has previously undergone oophorectomy on a nonevaluable basis usually should be treated with androgens or nonmasculinizing androgen derivatives (see p. 49) as the next form of systemic therapy. Exceptions may be made in patients with rapidly progressing disease, in which case a combination of cytotoxic drugs and hormones may be used, or in which the problem is mainly ascites or pleural effusion, in which case alkylating agents such as HN2 or thio-tepa should be used. If the patient did not benefit from oophorectomy, I would ordinarily not use androgens immediately but turn to cytotoxic drugs such as 5FU (Fig. 3-3) or thio-tepa. (5FU would be selected first because it does not produce permanent marrow suppression, a problem that is frequently encountered after therapy with alkylating agents.)

Adrenalectomy[31] is discussed more in the medical literature than it actually plays a role in clinical management, for the long-term consequences of adrenalectomy represent a significant problem in many patients. Even in the most favorable series of cases, benefits are seen in no more than 30% of patients who undergo adrenalectomy. Obviously in order to obtain the most likely benefit from this procedure, all of the criteria for adrenalectomy should be favorable.[74, 81, 108] This includes a long free interval,[126] metastases predominantly in bone, skin, and soft tissue, and prior favorable response to oophorectomy and androgen therapy. Of these predictive factors, the long free interval appears to be the single most important factor. In practice, adrenalectomy is performed only once or twice a year for metastatic adenocarcinoma of the breast in most major medical centers. Exceptions occur in centers that are investigating the procedure and its predictive factors or that have apparently observed a higher percentage of satisfactory results such as Memorial Hospital in New York City and Peter Bent Brigham Hospital in Boston.

It has been apparent that adrenalectomy does not interfere significantly with subsequent chemotherapeutic management, for a patient can be maintained on supplementary adrenal corticosteroids and simultaneously be treated with even the most toxic single or combination agents. Many surgeons have confirmed the safety of adrenalectomy and immediate therapy with 5FU, as described by Hall and Wilson.[48] However, this combination of adrenalectomy, oophorectomy, and 5FU has never been compared on a randomized basis with the same modalities used sequentially. The rationale for the combined method is also regarded skeptically by many endocrinologists and oncologists, because it appears difficult to justify oophorectomy in elderly women (up to age 72 years[126]), especially when vaginal cytologic examination reveals a lack of cornification, the patient has the physiognomy of advanced age, and the ovaries are found to be atrophic.

Treatment of metastatic carcinoma of the breast in the patient at or just

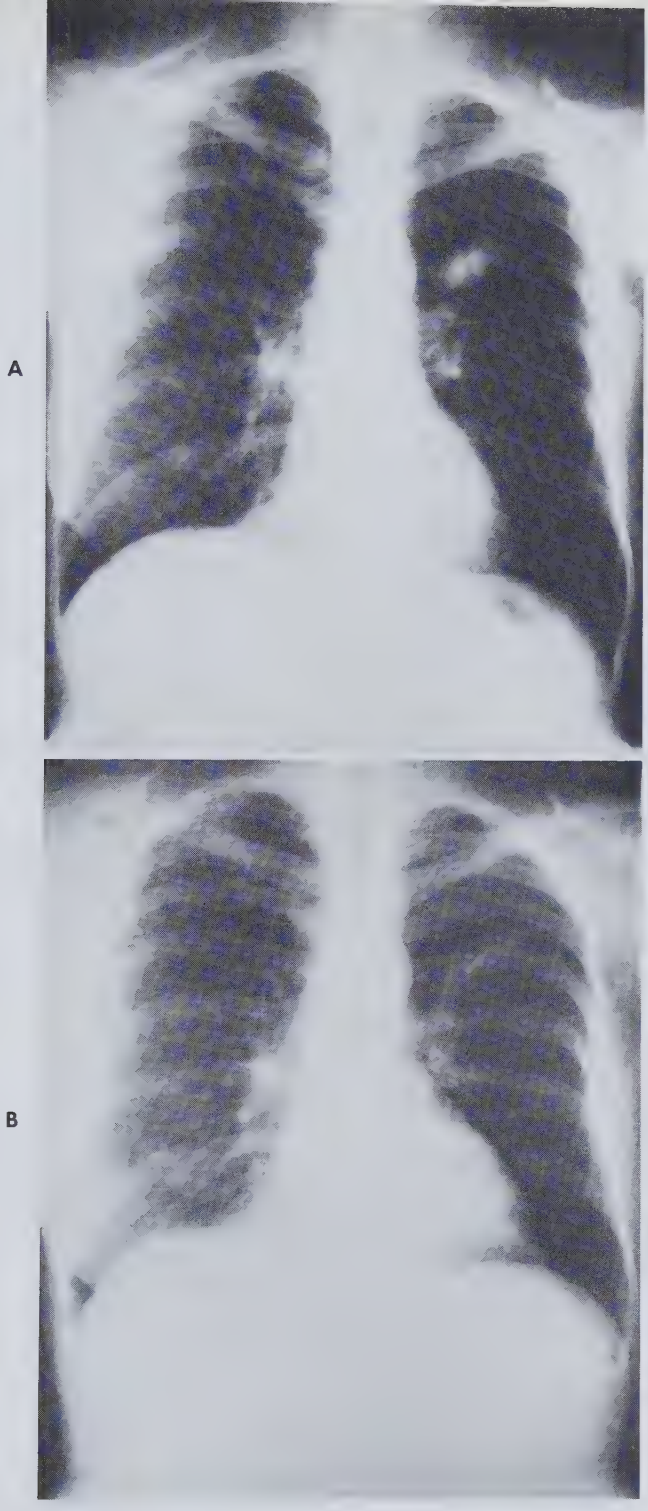

Fig. 3-3. Adenocarcinoma of breast metastatic to left upper pulmonary lobe in 35-year-old woman who also had supraclavicular metastasis and who failed to respond to oophorectomy. **A,** Pretreatment x-ray film. **B,** X-ray film taken after 3½ months of treatment with intravenous 5FU, 500 mg/week. Complete response occurred within 1 month and persisted for almost 1 year. Progression was then suspected because of signs and symptoms of spinal cord irritation.

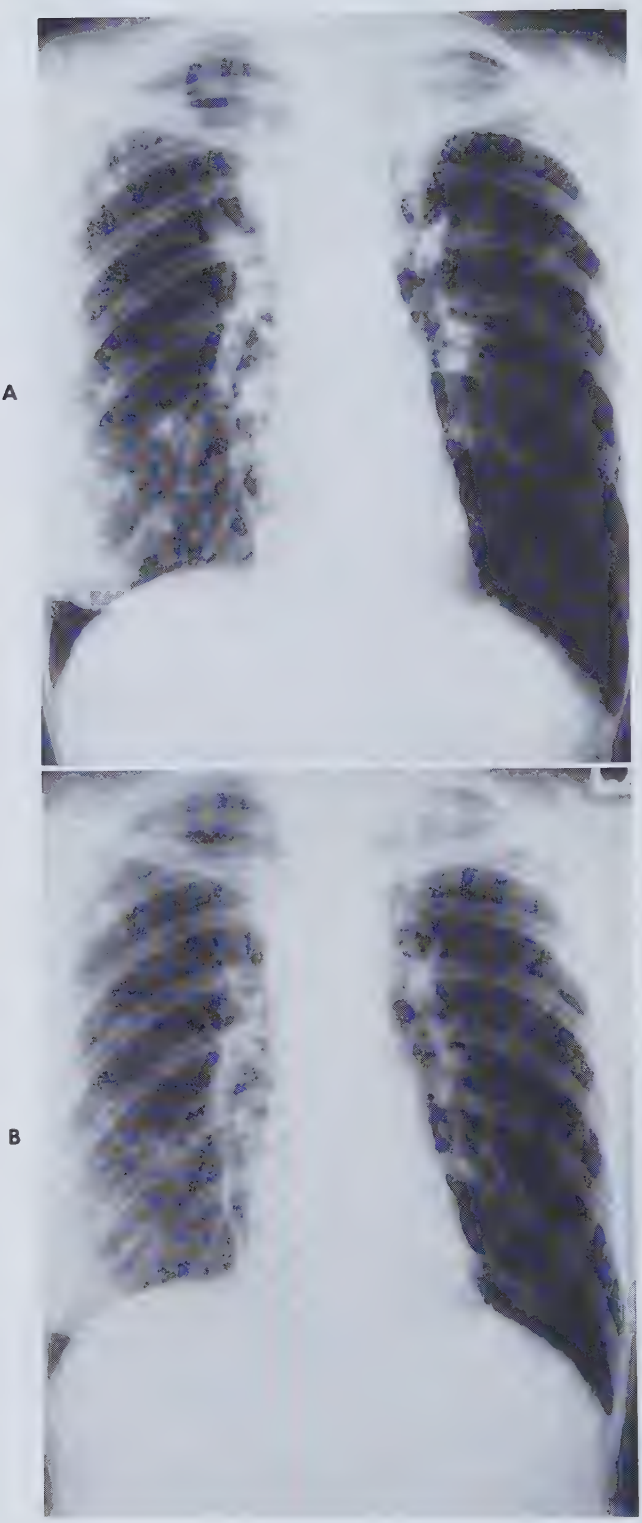

Fig. 3-4. For legend see opposite page.

beyond menopause or in whom menopause is difficult to assess because of prior hysterectomy is the most common and also the most difficult problem encountered in chemotherapy for carcinoma of the breast. In my experience, these patients usually respond poorly to androgen therapy. They frequently have rapidly progressive tumors and therefore are in a poor prognostic group for adrenalectomy. They often present with simultaneous disease in many deep viscera. Therefore I usually begin cytotoxic therapy immediately. The drug selected is either 5FU alone, for the reason previously mentioned, or the five-drug combination for patients who are either very ill or moribund when first seen (Fig. 3-4).

If the patient is, by history, 5 years or more past menopause (especially when hot flashes have been observed by the patient), estrogen therapy may be cautiously begun. However, the serum calcium must be watched closely, especially in patients who have bony metastases apparent on x-ray examination or scan, and the patient must be informed of the symptoms of hypercalcemia (drowsiness and nausea) so that she will return promptly rather than simply take estrogen therapy until dangerous levels of hypercalcemia develop. It is my impression that responses to estrogen therapy are increased and the danger of hypercalcemia or acceleration of tumor growth is diminished with increasing age of the patient. On the other hand, the troublesome or dangerous side effects of estrogen in elderly patients are also significant, including fluid retention and cardiac failure. The elderly woman will almost always show a good response to estrogen therapy, but treatment must be administered carefully to avoid serious anasarca or the surprising side effects of increased libido and vaginal bleeding.

It has recently been reported that the synthetic nonmasculinizing androgen calusterone (Methosarb)[12] causes responses in 40% of postmenopausal women with metastatic cancer of the breast. This includes patients in whom the menopause was induced by oophorectomy as well as those with a natural menopause. If these results are confirmed by subsequent clinical trials, this will be of great benefit in the management of this common and distressing disease, which is the most common cause of death from cancer in women.

Carcinoma of the breast in elderly men[28] has responded well to therapy with both chemotherapeutic agents and estrogens; metastatic carcinoma of the breast in men[115] has also responded well to endocrine ablative procedures.[57]

It should be emphasized that the patient with metastatic carcinoma of the breast has frequent episodes of pain from local disease, especially metastases in the femoral neck, spine, and brain. Radiation therapy is more useful than chemotherapy for such localized manifestations of metastatic cancer.

Fig. 3-4. Adenocarcinoma of breast metastatic to lungs and mediastinum with severe superior vena caval syndrome and dyspnea in a 55-year-old woman. **A,** Pretreatment x-ray film showing wide mediastinum, multiple pulmonary nodules, and fibrotic effect of prior irradiation in left upper lobe. Patient also had lymphangitic pulmonary metastases not seen clearly in this radiograph. **B,** Results of therapy with five-drug combination (see text) using 5FU, MTX, cyclophosphamide, vincristine, and prednisone. Shows complete resolution of nodules and disappearance of dyspnea and superior vena caval syndrome 2½ months later. Patient maintained complete response for 8 months, then gradually developed pituitary insufficiency as a result of brain metastases while remission of extracranial disease persisted.

Melanoma

The improvement in the chemotherapy of metastatic melanoma has been one of the most significant changes that has occurred in the past decade in the management of disseminated solid tumors. DTIC therapy produces responses in 25% of patients (Fig. 3-5), and approximately 10% of patients show complete response, with prolonged survival without therapy seen in 1% to 2% of these patients. Other patients respond to the nitrosoureas or to intralesional therapy with BCG.

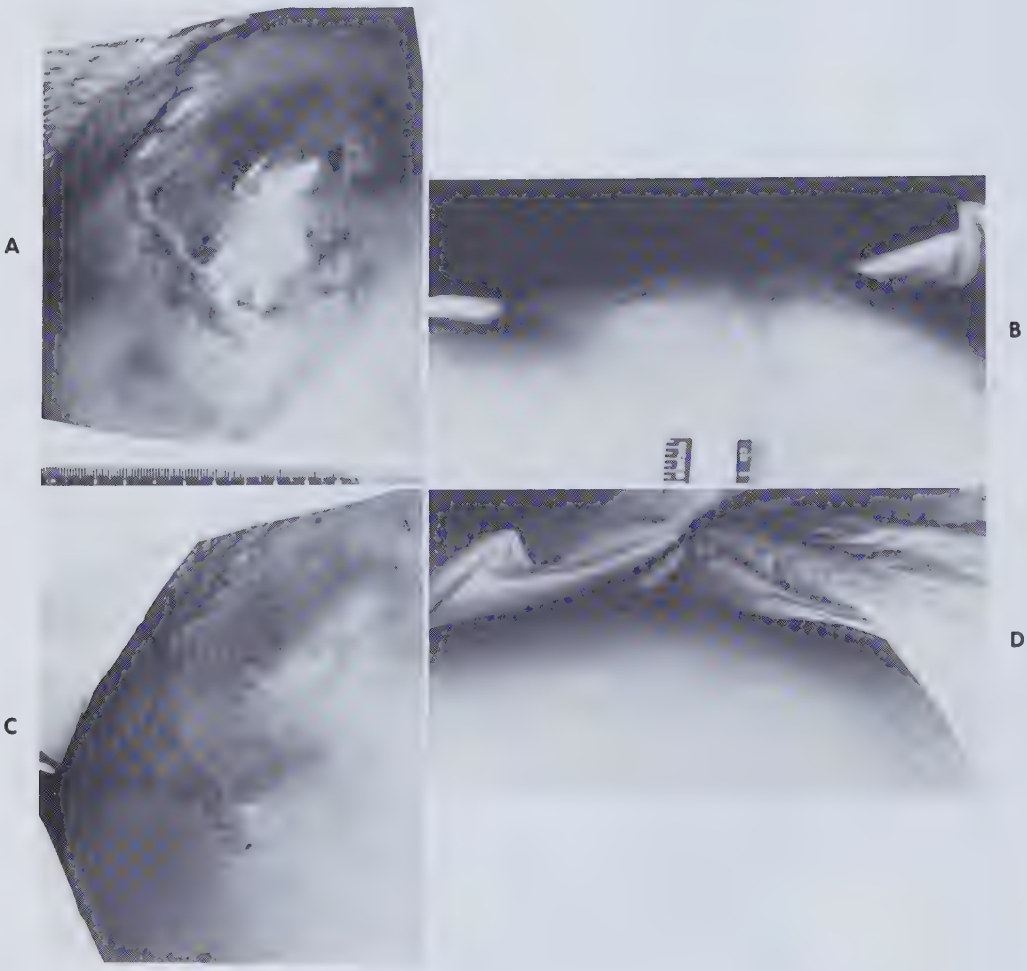

Fig. 3-5. Metastatic melanoma in a 32-year-old woman, 4 months pregnant, with widespread metastases (multiple breast, liver, skin, subcutaneous, pulmonary, and axillary metastases). Recurrence appeared in left groin, **A**, which shows impending ulceration on anterior view, **B**, and produced femoral nerve and vein compression. After DTIC therapy, patient had complete disappearance of all lesions except groin metastasis, which regressed partially, **C** and **D**, and remained stable, with no residual neurovascular compression. Male infant delivered 5 months later is now 4 years old and in excellent health. Patient developed brain metastases 5 months after delivery.

The patient with metastatic melanoma should now receive greater scrutiny than ever before, and a specialist in chemotherapy of this tumor should be consulted when a patient develops metastasis following primary therapy of the lesion. The postoperative adjuvant use of BCG by intradermal or scratch inoculation is under investigation and is perhaps more widely used than is appreciated at the present time. However, this therapy is not recommended except on an approved investigational basis, for the appearance of blocking antibodies and debilitating side effects may occur from BCG. It is conceivable that the patient may be harmed rather than helped by these immunologic efforts, especially if the disease is potentially curable by surgery alone.

Sarcoma

Sarcomas of the miscellaneous soft tissue types are still relatively resistant to chemotherapy. Control must still be achieved by radical surgery in most cases, although preoperative destructive radiation therapy may play a role, especially in the treatment of osteogenic sarcoma.[38] The patient with metastatic sarcoma should be treated by resection, if possible, especially if local metastasis or local recurrence appears. When distant metastatic disease appears—such as pulmonary metastases—surgery should still be considered, especially if the lesion is a solitary metastasis and no additional lesions have appeared within a suitable period, e.g., 6 weeks to 6 months. The likelihood of response to chemotherapy is probably no better than 20%, but the results can be exceedingly worthwhile in patients who do respond to chemotherapy.

It is my impression that chemotherapy should be instituted when incurable metastatic sarcoma is present and evaluable, even if asymptomatic, rather than waiting until the patient is symptomatic or moribund. The variable response to chemotherapy usually requires that the patient be treated in sequence with a variety of drugs or combinations. If the patient is first seen when only advanced disease is present, the opportunity to utilize all of these modalities is never achieved. I have observed excellent results in such unlikely situations as widespread leiomyosarcoma of the uterus, with a complete response to 5FU persisting after 3 years, MTX having been added for the past 1½ years, and osteogenic sarcoma metastatic to the liver, with excellent responses from cyclophosphamide and subsequently from DTIC, the duration of response persisting for more than 2 years. I have also observed occasional partial responses to actinomycin D and cyclophosphamide. Leiomyosarcoma has recently been reported to respond in an unusually specific fashion to the amino acid analogue cycloleucine (NSC 1026), although I was personally unable to see a response in eight patients treated with cycloleucine.

The recent experience with Adriamycin indicates that it is probably the most potent single agent available for the chemotherapy of sarcomas. Since it is not commercially available and since its toxicity is somewhat unusual, it is recommended that it be administered only by physicians who have experience in the management of chemotherapeutic drugs. It is mentioned in this section mainly to emphasize the role of chemotherapy, especially with Adriamycin, and to encourage oncologic consultation for patients with metastatic sarcomas early in the management of their metastatic disease.

Carcinoma of ovary

Carcinoma of the ovary is most commonly encountered as papillary cystadenoma of the ovary, although other, rarer forms are also seen. Teratomas are essentially unresponsive to chemotherapy. Embryonal carcinoma of the ovary probably should be treated in the same way as embryonal carcinoma of the testes. I have seen one good symptomatic and objective partial response in my only patient with metastatic embryonal carcinoma of the ovary, utilizing therapy with COMF (see protocol for COMF therapy on p. 59). Ovarian cancers are occasionally encountered by general surgeons when a patient presents with ascites, an abdominal mass, or colon obstruction of unknown cause. It is considered standard gynecologic management to perform total hysterectomy and bilateral salpingo-oophorectomy for such patients, along with removal of as much of the tumor as possible. General surgeons, on the other hand, appear reluctant to do such wide resective surgery in the presence of extensive metastases or peritoneal and small bowel implants. Having had patients referred from both general surgeons who have done only a biopsy and gynecologists who have done the wide palliative resection, it is difficult for me to conclude that the extensive palliative resection actually provides substantial benefit in these patients. The effect of chemotherapy can be surprisingly worthwhile even in the presence of extensive tumor, for if the drug is specifically useful, the tumor will recede remarkably. If chemotherapy is not useful, progression occurs rapidly whether hysterectomy and oophorectomy have been performed or not. Radiation therapy plays a significant role in the management of many of these patients, but total abdominal radiation produces a significant morbidity. I generally prefer to begin with chemotherapy, utilizing thio-tepa or CCNU and reserve radiation therapy for the treatment of local tumor masses at a later time. If palliative therapy for stage IV adenocarcinoma of the ovaries is begun with an intensive course of pelvic radiation therapy, subsequent chemotherapeutic management is always a difficult problem because of persistent leukopenia. On the other hand, full-dose pelvic radiation can be given following prolonged chemotherapy without incurring a serious risk of sepsis from leukopenia. I have recently seen a complete response in a patient with extensive carcinoma of the ovary treated with CCNU, who has had perfect control of the ascites and abdominal mass following a single dose of 100 mg/M^2. No side effects occurred with this therapy, and the patient was free of disease 8 weeks after drug administration, with a normal white count and platelet count. This result is similar to the effect that can be achieved from thio-tepa and chlorambucil in approximately 50% of patients, but therapy with thio-tepa or chlorambucil requires treatment on a continuous basis (weekly or daily, respectively).

Head and neck cancers

Squamous and undifferentiated cancers of the head and neck occur on the face and lip and in the paranasal sinuses, oral cavity, pharynx, hypopharynx, and larynx. These tumors have variable natural histories, but all are similar in their response to chemotherapy, with the possible exception of carcinomas of the maxillary antrum, which appear to be somewhat more susceptible to therapy. It is unknown whether this is because of the variable natural history of the squamous carcinomas or is a specific characteristic in tumors of the maxilla. Carci-

nomas of the maxillary antrum are also particularly accessible to infusion therapy through the branches of the external maxillary artery. I have seen responses in approximately 30% of 40 patients treated with MTX or 5FU in conventional systemic outpatient chemotherapeutic treatment of tumors of the head and neck. Responses occur in approximately 60% of patients with squamous cancer of the head and neck treated with a toxic MTX regimen.[70] Therapy with MTX or 5FU obviously is ultimately unsuccessful in most patients, but the temporary beneficial results of therapy can make this type of treatment encouraging to attempt.

Several examples can be given to illustrate the results and problems encountered. One of my patients had a complete response, sustained for 1 year, in a large submaxillary metastasis of carcinoma of the oral cavity treated with 5FU on a weekly outpatient basis. A similar regimen, 500 mg/week, was used to produce a complete response in recurrent carcinoma of the hypopharynx following previous radiation therapy and biopsy-proved recurrence. This patient was rendered asymptomatic, but ironically he then returned to his dollar-a-night boarding house and his excessive alcohol ingestion, failing to return for weekly injections. Eventually he suffered a relapse and died. Control in this case was achieved for more than 3 months; the potential duration of control could not be assessed because of the patient's desire to withdraw again from society.

In another patient a complete remission occurred in a maxillary antral carcinoma eroding through the hard palate within the first 4 days of infusion therapy with 5FU given through the superficial temporal artery. This therapy was subsequently followed by radiation treatments and radical maxillectomy. The patient remained free of disease 2 years later when last seen.

A nearly complete disappearance of large pulmonary metastases occurred in one patient with carcinoma of the larynx and in a patient with carcinoma of the epiglottis, both of whom received MTX. In the first case the patient was essentially free of disease when he returned to his psychologic pattern of alcoholism and withdrawal several months later, from which he died. The second patient eventually died of a myocardial infarction and stroke. Thus the benefits of chemotherapy were somewhat academic in both instances. Other such cases have been observed that indicate that chemotherapy is of excellent technical benefit but the overall management of patients with carcinomas of the oral cavity can be unrewarding because of the underlying associated diseases. On the other hand, considerable benefit was achieved—but not from chemotherapy—in a patient referred for management of extensive recurrence of carcinoma of the lip involving the mandible and submaxillary glands. He had previously undergone several operations and two courses of radiation therapy. I elected to treat him with wide reexcision of the lower face, lip, and mandible, and performed a radical neck dissection. The patient was rendered free of disease and returned to a productive life as an owner-manager of a large grain storage elevator for the ensuing 4 years until his sudden death from a myocardial infarction.

Chemotherapy for head and neck cancers must therefore be managed in cooperation with radiation therapy and surgery and every effort made to render the patient free of disease by combined therapy rather than to consign the patient to palliative chemotherapy alone. Other carcinomas of the head and neck provide specific problems, for which answers must be selected on an empirical basis.

Adenocarcinoma occurs in the sinuses and in the minor salivary glands. This type of tumor probably should be treated with 5FU when distant metastases occur. Carcinoma also may occur in patients who have previously been reported to have benign mixed tumors of the submaxillary or parotid gland. I have seen two such patients, one of whom failed to respond to all chemotherapy, but the other responded well for more than 2 years with the five-drug combination utilized for carcinoma of the breast. He had a complete response of a large cervical lymph node and showed stabilization of previously progressive pulmonary metastases. It was nevertheless a perfect symptomatic result, and the patient returned to full-time work during the period of his remission.

Carcinomas of the thyroid are essentially totally unresponsive to chemotherapy and should be treated with appropriate surgery, radiation therapy, and radioisotope management.[120] Thyroid hormone is useful in depressing the growth of well-differentiated thyroid cancers in many patients. I have also treated one patient with an undifferentiated carcinoma of the thyroid, following tracheostomy and local ^{60}C irradiation. She was given 5FU weekly and was free of recurrence with the tracheostomy closed 1½ years later when last contacted.

The dramatic, potential long-term effects of sequential combined management were observed in another patient treated initially for a mixed follicular and papillary carcinoma of the thyroid in 1949. This patient, then aged 19 years, presented with large metastases in the left neck and extensive pulmonary metastases. A palliative thyroidectomy and left radical neck dissection were performed at the Colorado General Hospital. She was subsequently treated repeatedly with therapeutic doses of ^{131}I and 5 grains of thyroid hormone per day. Her pulmonary metastases gradually regressed and had completely disappeared by 1969, at which time she had raised several children of her own and was in perfectly good health, free of disease.

Carcinoma of the parathyroid glands[107] presents the problem of hypercalcemia, which is more likely to be relieved by the usual methods for lowering serum calcium (see the discussion of mithramycin[96]) than by specific cancer chemotherapy.

Carcinoma of kidney

Adenocarcinoma of the kidney is occasionally encountered by general surgeons because of metastases that may occur far from the primary tumor. The patients may present with fever of unknown origin, abdominal pain, or pulmonary, bony, or soft tissue metastases that create a problem in diagnostic evaluation. Any undifferentiated cancer should be considered possibly of renal origin until selective renal arteriography has been performed. Obviously the other possibilities in undifferentiated cancers include reticulum cell sarcoma, amelanotic melanoma, carcinoma of the lung, and the puzzling undifferentiated carcinomas of unknown primary site. When hypernephroma has been documented, I recommend that nephrectomy be performed in most cases, even when widespread metastatic disease is apparent. The natural history of hypernephroma is extremely variable, with some patients exhibiting long periods of spontaneous lack of growth of the tumor and others exhibiting either spontaneous partial or—rarely—complete remission. I have seen several patients with hypernephroma with either long-standing stability of metastases or cure resulting from resection

of multiple metastases, and I therefore encourage removal of the primary tumor for whatever benefit it may confer. Remission after resection of the primary tumor has been reported, and certainly removal of the primary tumor prevents growth into the parietes with the associated pain, abscess, and danger of hemorrhage.

Drug treatment of hypernephroma has been notoriously unsuccessful, although there were reports of dramatic benefit from androgens and progestins some years ago.[7] I have seen one excellent evaluable response to long-term androgen therapy in a patient with a large pulmonary metastasis; a similar result occurred over a period of 12 months in a patient who received 5000 mg of Delalutin weekly. On the other hand, more than a dozen other patients have failed to respond to androgens, progestins, or both. I have seen one excellent evaluable response for approximately 4 weeks from DTIC, but no other chemotherapeutic agents have been helpful in my patients.

Current management of metastatic hypernephroma with drug therapy is therefore recommended to be hormone management initially followed by investigational drugs[89] when the patient develops early symptoms and has objectively evaluable metastases.

The less common forms of cancer of the kidney in adults are essentially never encountered by general surgeons. Patients with metastatic embryonal carcinoma of the kidney (Wilms' tumor) should be referred to a pediatric oncologist for actinomycin D therapy or combined therapy according to the current pediatric oncologic protocols. Transitional cell carcinoma of the renal pelvis, as with transitional cell carcinomas elsewhere in the urinary tract, has been almost completely resistant to chemotherapy. However, Adriamycin has been reported to be of some benefit to patients with transitional cell carcinomas. I have seen apparent partial regression in two patients with recurrent carcinoma of the bladder metastatic in the lower abdominal soft tissues, and I recommend Adriamycin therapy for such patients. Thio-tepa has also been used with apparent success in bladder irrigations for patients with recurrent low-grade papillary carcinoma of the bladder. Doses of 30 to 60 mg are instilled on a weekly basis for 4 weeks in such patients, and many long-term remissions have been described following such therapy. Therefore thio-tepa would be an appropriate drug to consider in transitional cell carcinomas of the other areas of the urinary tract.

Testicular tumors

Testicular tumors represent a rare but occasional problem for general surgeons. The management of these patients is usually carried out by urologists, radiation therapists, and oncologists.[58] It should be emphasized that the treatment of seminoma is still radical surgery and radiation therapy with a 90% to 95% likelihood of cure being achieved. When a patient with seminoma shows metastatic disease at a later time, it is usually not metastatic seminoma but another germ cell type that is found.

Management of metastatic carcinoma of testicular origin therefore presupposes that the patient has one of the nonseminomatous types of tumor, including elements of embryonal carcinoma, teratocarcinoma, choriocarcinoma, or all three. I obtain determinations of urinary gonadotropin levels on a weekly basis throughout therapy, because these levels may become positive at any time in

such patients. The quantity of hormone excreted is one of the best indications of the response or failure of response to therapy.

In my treatment of 12 patients with metastatic nonseminomatous carcinomas of the testes I have utilized a sequential program of actinomycin D[83] followed by VCFM,[88] followed by bleomycin (with or without vinblastine)[113] or mithramycin,[55] depending on the patient's bone marrow reserve[69] at the time of completion of VCFM therapy. One patient with pulmonary metastases of teratocarcinoma responded completely to actinomycin D and remains in complete remission 3 years after therapy was instituted. I have had partial responses in tumors of various mixed types with actinomycin D.

I believe that the combination of bleomycin and vinblastine may be the best type of therapy available for control of actinomycin D–resistant testicular tumors at the present time. It is, however, unacceptably toxic for many patients, and VCFM produces substantially less toxicity. Actinomycin D and triple therapy (actinomycin D, MTX, and chlorambucil)[2] have been the traditional initial modalities of chemotherapy for testicular tumors. A National Cancer Institute study currently under way is designed to determine whether actinomycin D alone is superior or inferior to triple therapy. Until the study is completed, I will continue to utilize actinomycin D alone for simplicity and safety.

All patients with unresectable metastatic carcinoma of the testes should receive intensive chemotherapy because of the possibility of cure even when widespread disease is present. However, the extent of disease and the patient's general state of health are clearly important predictive factors in success of this treatment. The role of mithramycin appears limited to the treatment of embryonal carcinoma, although it has occasionally been reported to produce responses in other types of testicular tumors as well.

SUMMARY

Increasing awareness of the various modalities of cancer therapy by patients and physicians makes it essential for surgeons to be aware of the current status of cancer chemotherapy. Some of the patients with poor prognosis or obvious metastases can be treated by the relatively simple guidelines outlined in this chapter, whereas in other circumstances the treatment is so complex that only the indications for therapy can be successfully outlined in print.

It is obvious that early referrals for consultation regarding chemotherapy are important, so that the patient's condition is not moribund when first considered as a candidate for chemotherapy. The patient and his family must understand the purpose and nature of the treatment, and the physician must be honest with himself and his patients, utilizing careful records and common sense as his best guides to therapy.

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4

Obstructions of the colon

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One of the most conspicuous problems in the management of obstruction of the colon is that no single surgeon encounters many cases.[30] Patients treated for obstruction of the small intestine outnumber those treated for obstruction of the colon by a ratio of 7:1. However, lack of experience by the individual surgeon is not the only reason for the high mortality[2, 24, 27] in obstruction of the colon. There are other basic reasons, i.e., the advanced age of many of the patients, the poor general condition of the patients, delayed diagnosis,[17] and errors in diagnosis and therapy.[28]

Colon obstructions[34] differ in many respects from obstructions of the small intestine (Table 4-1). It is surprising to note in how many reports on intestinal obstruction, often from excellent institutions, the differences between colon obstructions and obstructions of the small intestine are not emphasized. There are striking differences in etiology (Table 4-1). Colon obstructions most often occur in older patients. Serious electrolyte imbalances are common in obstructions of the small intestine, whereas these are uncommon in colon obstructions. The patient with a colon obstruction is usually a poor surgical risk because of long-standing disease. This is usually not true in obstructions of the small intestine. For example, anemia, hypoproteinemia, blood volume deficits, and systemic problems (vascular disease, etc.) are common in colon obstruction but unusual in obstructions of the small intestine.

In the common types of colon obstruction (primary carcinoma,[32] volvulus, and diverticulitis) the therapy is basically different from the treatment of small bowel obstruction.[27] Generally a procedure is done that will quickly relieve the obstruction. No attempt is made at the original operation to eliminate the cause of the obstruction. On the other hand, one operation for obstruction of the small

Table 4-1. Differences between obstructions of colon and small intestine

	Small intestine	Colon
Etiology	Adhesions, external abdominal hernias, etc.	Primary carcinoma, primary volvulus, diverticulitis, secondary carcinoma, etc.
Electrolyte deficiences	Common	Uncommon
Associated systemic diseases	Uncommon	Common
Anemia hypoproteinemia	Uncommon	Common
Previous abdominal symptoms	Uncommon	Common
Clinical onset	Sudden	Usually gradual
Vomiting	Common	Uncommon
Degree of distention	Variable	Usually severe
Treatment	One operation	Usually two or three operations

intestine will usually not only relieve the obstruction but will also eradicate the cause of the obstruction. Most of the experience of individual surgeons is with small bowel obstructions. Experienced surgeons may commit both diagnostic and therapeutic errors if they do not constantly remind themselves of the possibility of a colonic obstruction and its completely different problems.

ETIOLOGY

Colon obstructions differ markedly from small bowel obstructions in many aspects.[31] One of the most striking differences is in etiology. Primary carcinoma[26] of the colon is the most common cause of colon obstruction, accounting for 75% to 80% of cases. On the other hand, primary carcinoma of the small intestine is a relatively rare cause of obstruction of the small intestine, occurring in only 1% of cases. Primary volvulus (i.e., twisting of the bowel not occurring around an adhesion) of the colon[1, 20] (particularly in the sigmoid) is a common cause of colon obstruction (15% to 20%). Primary volvulus of the small intestine is rare, midgut volvulus in the infant being the only type that occurs with any frequency. This causes less than 1% of all small bowel obstructions. Inflammatory conditions of the colon (i.e., diverticulitis[16]) are a relatively common cause of obstruction of the colon (5% to 10%). On the other hand, inflammatory conditions of the small intestine (Crohn's disease, etc.) rarely cause obstruction of the small intestine (1%). The fourth most common cause of obstruction of the colon is primary or secondary pelvic organ carcinoma, usually in the female (uterine, ovarian, etc.). This etiology is a much less common cause of obstruction of the small intestine.

It is evident, also, that the conditions that cause obstruction of the small bowel rarely cause obstruction of the colon. Adhesions, usually postoperative, are the most common cause of small bowel obstructions. Adhesions rarely cause obstruction of the colon. Incarcerated external abdominal hernia is the second most common cause of small bowel obstruction. This etiology rarely causes colon obstruction. Primary intussusception (colocolic) of the colon is a rare cause of colon obstruction. On the other hand, primary intussusception (i.e., intussusception not associated with Meckel's diverticulum, benign or malignant neoplasm, etc.) is a relatively common cause of small bowel obstruction. This is usually of

the ileocecal type. Secondary intussusception precipitated by Meckel's diverticulum, benign or malignant neoplasm, duplication, etc. is not uncommon as a cause of small bowel obstruction. Secondary intussusception of the colon precipitated by a benign or malignant neoplasm, duplication, etc. rarely occurs (1%).

Internal hernia as a cause of intestinal obstruction can be either primary, i.e., paraduodenal fossa, etc., or secondary (iatrogenic), through an opening in the mesentery, mesocolon, or omentum produced by an operative procedure. Internal hernias of both types not infrequently cause obstruction of the small intestine. This etiology is a rare cause of colon obstruction. However, diaphragmatic hernia, congenital or traumatic, can cause either obstruction of the small intestine or colon or both simultaneously. Both large and small bowel are involved with equal frequency. The overall incidence is low (1%). An interesting type of colon obstruction caused by diaphragmatic hernia is herniation of the splenic flexure through the foramen of Bochdalek.

Intraluminal foreign bodies (gallstones, bezoars, etc.) not infrequently will obstruct the small intestine, particularly the terminal ileum. These practically never obstruct the colon. If a foreign body is small enough to pass through the ileocecal valve, it will usually not obstruct the colon.

Acute inflammatory conditions of the peritoneal cavity not infrequently cause obstructions of the small intestine. When this occurs it is most often caused by pelvic inflammatory disease, complicated cholecystitis, or complicated appendicitis. Less frequently is the colon obstructed. Acute inflammatory disease of the intestine (exclusive of colon diverticulitis) is an unusual cause of obstruction of either the large or small intestine. Crohn's disease of the small intestine occasionally manifests itself as intestinal obstruction. Crohn's disease of the colon (granulomatous colitis) or ulcerative colitis rarely causes obstruction of the colon.

Atresia of the small intestine is a relatively common cause of small bowel obstruction in newborn infants. Atresia of the colon is much less common and usually occurs concurrently with atresia of the small intestine. Duplication can occur anywhere in the gastrointestinal tract. This is an occasional cause of small bowel obstruction in infants and less common in older children and adults. Duplication as a cause of colic obstruction is extremely rare. However, disorders of rotation of the intestine (malrotation, incomplete rotation, etc.) are not uncommon as a cause of obstruction of the small intestine in infants. Examples of this are extrinsic duodenal obstruction and midgut volvulus. These disorders of rotation rarely cause colon obstruction.

Meconium ileus occasionally produces obstruction of the small intestine in infants. This etiology rarely produces colon obstruction. Endometriosis involving the sigmoid colon can cause obstruction of the colon. This condition rarely causes obstruction of the small intestine. Splenosis can cause small bowel obstruction. Rarely, if ever, does it cause colon obstruction.

Arterial occlusion (thrombosis or embolus) as a cause of obstruction usually involves the superior mesenteric artery or the branches thereof and not infrequently causes obstruction of the small intestine. Rarely does arterial obstruction of the colic vessels produce colon obstruction.

Prolapse of the stoma of a colostomy or ileostomy can produce intestinal

obstruction. The former occurs more often because of the large number of colostomies that are performed.

From this discussion, it is evident that from an etiologic standpoint there are many differences between obstructions of the small intestine and obstructions of the colon.

AGE AND SEX

Colon obstructions occur primarily in older patients. This is because the common conditions that cause colon obstruction, i.e., carcinoma of the colon, colon volvulus, diverticulitis, and extracolic pelvic carcinoma, are diseases of middle-aged and older patients. In our experience these four conditions cause over 95% of colon obstructions.

On the other hand, small bowel obstruction occurs in all age groups. However, there is a slight predominance of small bowel obstruction in middle-aged and older people. This is because of the large number of individuals of all ages who now have abdominal operations and are therefore subject to small bowel adhesive obstructions. Volvulus of the sigmoid colon is the only type of colon obstruction in which the sex of the patient plays a part in the occurrence of the obstruction. A redundant sigmoid colon occurs with equal incidence in both elderly males and females. However, if torsion occurs, spontaneous derotation is more apt to occur in the female because of the relatively larger size of the female pelvis.

GENERAL CONDITION OF PATIENTS

In general, patients with colon obstructions are poorer surgical risks than patients with small bowel obstructions. This is related to etiology and age. As stated previously, the most common cause of colon obstruction (75% to 80%) is carcinoma of the colon. The carcinoma has usually been present for many months but has been relatively silent until colon obstruction occurs. Anemia is common in such patients, occurring in 20% of patients in our series. We also found that 15% of patients had serious serum protein deficits, and 30% had demonstrable metastatic disease.[24, 30] In addition, there were the usual cardiovascular problems common in the age group affected. Volvulus of the sigmoid colon occurs primarily in elderly males, although it does occur in females.[1, 29] These patients often reside in nursing homes or mental institutions where nutrition may not be of the best quality, and attention to bowel elimination is often inadequate. Prolonged constipation leads to elongation of the sigmoid colon, which increases the chance of torsion. The patient with colon diverticulitis and obstruction is often in somewhat better condition than the patient with obstructing carcinoma. However, he usually does have the lowered body resistance that accompanies chronic infection. The patient who has a colon obstruction resulting from an extracolic, pelvic neoplasm suffers from an extensive malignant process and the resulting systemic problems.

Signs and symptoms of colon obstruction

The classic signs and symptoms of colon obstruction are cramping abdominal pain, nausea, inability to defecate or expel flatus, progressive abdominal distention, and occasionally vomiting. The clinical picture often differs from that

presented by an acute small bowel obstruction. Usually in colon obstructions the onset is insidious and gradual as compared to the frequently sudden, dramatic onset of small bowel obstruction. Vomiting is less severe and not infrequently absent in colon obstructions. This applies even in far-advanced colon obstructions. The degree of distention in colon obstructions is usually more severe than in small bowel obstructions.

A careful history in colon obstructions, particularly in obstructions due to colon carcinoma, is often revealing and suggestive of the etiology. This is also frequently true in the other common types of colon obstruction, i.e., volvulus, diverticulitis, and extracolic pelvic malignancies.

Fig. 4-1. Volvulus of right colon.

Electrolyte abnormalities and other laboratory findings

It is interesting that electrolyte problems are usually not as severe in colon obstructions as in small bowel obstructions. Nevertheless, patients with colon obstructions do have to be carefully evaluated from an electrolyte standpoint. Deficiencies should be corrected as rapidly as possible, preferably before an operative procedure is performed. Patients with malignant obstructions of the colon are often anemic and have blood volume and serum protein deficits.[6, 9, 21] Obstructions caused by diverticulitis may reveal these same findings in addition to fever, leukocytosis, and other evidence of infection. Colon obstruction most often occurs in middle-aged or elderly patients in whom cardiovascular and

Fig. 4-2. Volvulus of sigmoid colon.

chronic obstructive respiratory problems are common. These should be carefully evaluated prior to an operative procedure.

DIAGNOSIS

A correct preoperative diagnosis of colon obstruction can practically always be made if certain principles are carefully followed.[1] When a colon obstruction is suspected, a nasogastric tube with suction should immediately be inserted to decompress the stomach and to prevent vomiting (and possible aspiration) while other diagnostic procedures are being performed. A no. 18 rubber (Levin) tube or plastic tube is preferable in the adult. Rectal digital examination is also indicated.

The next diagnostic step is to take plain (erect and supine) x-ray films of the

Fig. 4-3. Obstruction of splenic flexure caused by carcinoma with marked distention of cecum.

abdomen.[22] If the patient's general condition does not permit this, lateral decubitus x-ray films can be substituted for the erect films. Careful and meticulous interpretation of these films will usually lead to a diagnosis of colon obstruction (Figs. 4-1 and 4-2). The specific gas patterns of different parts of the small intestine and colon have been well documented by Wangensteen,[28] Cantor et al.,[6] and others.[26] If the plain x-ray films of the abdomen suggest colon obstruction, a proctoscopic (or colonoscopic) examination should then be done. Because most colon obstructions are low in the descending colon, the specific level of the obstruction can usually be determined by biopsy. Also, if sigmoid volvulus is present, the proctoscopic procedure may be of therapeutic value. If the plain x-ray films of the abdomen and proctoscopic examination do not definitely determine the level

Fig. 4-4. Obstruction of rectosigmoid caused by carcinoma.

and etiology of the colon obstruction, a barium enema should then be carefully performed as an emergency procedure. There is some slight risk of colon perforation if the colon obstruction is due to diverticulitis. However, this risk is minimal if the barium enema is given carefully with a minimal amount of pressure. The information to be obtained from the barium enema far outweighs the slight danger of perforation.

The termination of the barium enema column exhibits characteristic findings in each of the three common types of colon obstruction, i.e., carcinoma, volvulus, and diverticulitis. With the added information obtained from the enema, the presence, level, and probable etiology of the colon obstruction can practically always be determined (Figs. 4-3 to 4-5).

Fig. 4-5. Barium enema in sigmoid volvulus.

ROLE OF ILEOCECAL VALVE

Any discussion of obstructive lesions of the colon must take into consideration the physiology of the ileocecal valve. According to Cantor et al.,[6] distention of the small bowel as noted radiologically has been found to be present in only 30% to 40% of all colon obstructions. Marked small bowel distention is far more likely to be found in obstructive lesions of the ascending colon, particularly those involving the ileocecal valve. The usual etiology is primary colon carcinoma in the cecal area or right colon ("cecal") volvulus.

There is a diversity of opinion concerning the incidence of competence of the ileocecal valve. Cantor et al.[6] found that this valve was competent in 61% of patients with colon obstructions. The competence or incompetence of the ileocecal valve is of importance in evaluating the radiologic findings as well as in determining the type of treatment to be instituted, i.e., whether or not a long intestinal tube should be part of the treatment. Competence of the ileocecal valve creates a closed-loop obstruction. In such cases there is a definite danger of cecal perforation. According to Cantor et al.,[6] the anatomy of the ileocecal valve is such that the distention of the cecum, by stretching the lips or folds above and below the valve, tends to increase its competence. They further suggested that the ileocecal valve is subject to neurologic control. The competence of the valve does seem to depend, to some extent, on the tonicity of the fibers of the sphincter. The tonus of the sphincter has been increased experimentally by stimulation of the sympathetic nerves. Also, stimulation of the distal part of the colon increases the back pressure by approximately three times the normal sphincter back pressure. These studies suggest that the resistance of the ileocecal sphincter to back pressure is increased by intraluminal pathologic conditions of the distal colon. Stimulation of the distal part of the colon, acting through Auerbach's plexus, is believed to increase the tonus of the ileocecal sphincter, making it more competent. These observations apparently support the assumption of danger of closed-loop obstruction of the colon and the predisposition to cecal perforation in association with a competent valve (Fig. 4-6). On the other hand, during the performance of a routine barium enema without colon obstruction being present, radiologists report that 60% to 90% of valves are incompetent. This high percentage of incompetency of the ileocecal valve is contrary to our experience with colon obstruction. Our opinion is that approximately 50% of the valves are competent in such cases.

Cecal perforation is a real danger in prolonged obstruction of the colon. Overdistention of the cecum results in compression of the intramural vessels, focal areas of gangrene, and resulting perforation. Diagnostically, if there is perforation of the cecum secondary to distal colon obstruction, the survey film of the abdomen usually reveals large amounts of subphrenic air (pneumoperitoneum). In some cases of cecal perforation, however, there may be no pneumoperitoneum. Probably this is the result of walling off of the perforation by the omentum or by localized distended loops of small intestine. In any case, when cecal perforation is present the colon may or may not be markedly distended, depending on the size of the perforation. Perforations are often small and may be pinpoint sized. Occasionally there are multiple small perforations. These perforations are usually, but not always, on the anteromedial aspect of the cecum. Associated small bowel distention is the result of paralytic ileus caused by the accompanying peritonitis.

If the ileocecal valve is competent and the colon obstruction far advanced,

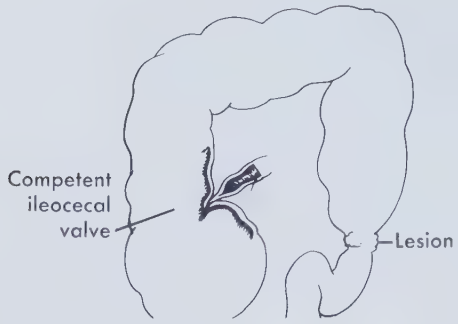

Fig. 4-6. Closed-loop obstruction of colon.

associated small bowel distention may be present without cecal perforation. As an additional obstructive factor, the small bowel may be distended for mechanical reasons if it is adherent to a carcinoma or an area of diverticulitis. Prior to actual perforation of the cecum, there are signs and symptoms in the lower right quadrant similar to appendicitis. There is also marked localized distention of the cecum in the lower right quadrant on x-rays films (Fig. 4-3). Cecal perforation presents a real danger in colon obstruction, particularly in obstructions due to carcinoma. Many patients with prolonged colon obstructions die as a result of cecal perforation.

TREATMENT

In the treatment of colon obstructions,[23] some type of primary decompressing procedure is usually done, and no attempt is made initially to eradicate the cause of the colon obstruction.[24] It is anticipated that a second procedure will be done later when the patient's general condition improves and when the colon can be properly prepared. There are exceptions to this general rule that will be detailed later.

In addition to operative treatment, attention should be given to any electrolyte, protein, and hemic deficiencies and any other problems in order to improve the general condition of the patient with any type of intestinal obstruction. Long intestinal tubes (Miller-Abbott, Cantor, Leonard, etc.) are of little value in colon obstructions because small bowel distention usually does not present a serious problem.

Primary colon carcinoma. The most common cause (75% to 85%) of colon obstruction is primary colon carcinoma.[5, 12] Of these obstructions, 85% occur in the left colon and rectosigmoid. The reasons for this are as follows: (1) Most colon carcinomas occur in the left colon. (2) The annular type of carcinoma is more common in the left than in the right colon. (3) The left colon, particularly the rectosigmoid area, has the smallest lumen of the large intestine. (4) The left colon has a thicker muscular wall and is less distensible than the right colon. (5) The fecal stream in the left colon is solid and adds to the obstructive process.

Cecal carcinoma. Cecal carcinoma obstruction is rare. When it occurs, the neoplasm usually encroaches on the ileocecal valve. The treatment of choice is

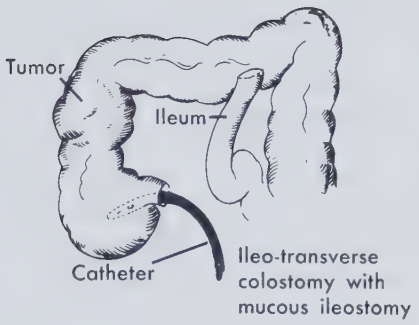

Fig. 4-7. Acute malignant obstruction of right colon.

primary resection of the right colon, the right transverse colon, and part of the terminal ileum. The anastomosis should be established between the end of the ileum and the side of the transverse colon. The blind end of the transverse colon is closed with inverting sutures.

In the poor-risk patient an ileotransverse colostomy is indicated (Fig. 4-7). The ileum is transected and the proximal end is anastomosed to the midtransverse colon (end to side). The distal ileum is brought out as an ileal mucous fistula, preferably through a small McBurney incision. A tube is passed through the distal ileum into the cecum for immediate decompression. In such cases, right colectomy and removal of the terminal ileum are performed after a period of 2 weeks when the patient's general condition has improved.

Carcinoma of ascending colon and hepatic flexure. In carcinoma of the ascending colon and hepatic flexure, primary resection is the treatment of choice, using the same technique as in obstructing cecal carcinoma. However, if the patient's general condition is poor, ileotransverse colostomy is indicated, using the same technique as in cecal carcinoma (Fig. 4-7). If the obstruction is at the hepatic flexure, cecostomy may be adequate for immediate decompression.

Carcinoma of transverse colon (exclusive of splenic flexure). In obstruction due to carcinoma of the transverse colon,[32] cecostomy is the treatment of choice. The cecostomy can be one of two types: tube cecostomy (Fig. 4-10) or exteriorization cecostomy (Fig. 4-9). The latter is the preference of one of the authors (MLM). It gives better decompression and defunctionalization. Excision of the fistula created by cecostomy can be done later (in about 2 weeks) when an ileocolectomy is also performed. This differs from the procedure done for cecal carcinoma in that the anastomosis should be from the ileum to the mobilized splenic flexure or proximal descending colon (end of ileum to side of colon).

Carcinoma of splenic flexure, descending colon, and rectosigmoid (left colon). There are three operative procedures that can be done in carcinoma of the splenic flexure, descending colon, and rectosigmoid, a common type of colon obstruction. These are tube cecostomy, exteriorization cecostomy, and right transverse colostomy (Fig. 4-1). We do not believe that a primary colectomy is indicated in the presence of acute obstruction of the left colon, except in instances where a perforated carcinoma may be present.

Of the three procedures listed, tube cecostomy is the most simple. However,

it does not allow as much decompression and defunctionalization as an exteriorization cecostomy or right transverse colostomy. Furthermore, tube cecostomy needs careful, detailed attention by the nursing staff, which unfortunately is not always available. A fistula created by tube cecostomy will usually close spontaneously after a left colectomy has been performed. Right transverse colostomy is a good procedure that gives the maximum degree of decompression and defunctionalization. However, a third operative procedure is necessary for closure of the stoma. Colcock[8] and an overwhelming number of surgeons prefer the right transverse colostomy in this type of colon obstruction.

Colon volvulus. Colon volvulus[29] is a relatively infrequent cause of intestinal obstruction among persons in the United States and in western Europe. It accounts for about 10% of patients with colon obstructions. Colon volvulus most often occurs in the sigmoid colon and in the right colon (incorrectly called "cecal volvulus"). In these areas the points of fixation of the colon are relatively close together, allowing colonic torsion to occur (Fig. 4-10). Volvulus of the transverse colon[21, 35] rarely occurs because of the relatively long distance between points of posterior fixation (i.e., hepatic and splenic flexures). Sigmoid volvulus usually occurs in elderly people. This is probably due to the fact that it takes many years to produce the redundancy of the colon necessary for volvulus to occur.

RIGHT COLON (CECAL) VOLVULUS. Right colon (cecal) volvulus can occur at any age (Fig. 4-1). The etiology is a congenitally long, narrow right mesocolon.[4, 15, 33, 37] The treatment of choice in right colon volvulus[25] is resection of the terminal ileum and right colon, with an end-to-side ileotransverse colon anastomosis.

VOLVULUS OF SIGMOID COLON. The sigmoid colon is the most common portion of the large intestine in which obstructing volvulus occurs. Volvulus of the sigmoid colon is becoming increasingly common in this country as people live longer. It is very common in middle and western Europe, where a high-residue diet is customary. This type of volvulus is frequent in patients in nursing homes and mental institutions. Apparently careful attention to bowel evacuation is neglected in such institutions, this being an etiologic factor. As mentioned previously, the condition is more common in males because of the relatively smaller size of the male pelvis.

The clinical picture is characterized by the insidious onset of cramping abdominal pain, inability to expel flatus or pass feces, and progressive abdominal distention, which often becomes very marked.

Radiologically there is a marked distention of a closed loop of the left colon that may extend as high as the diaphragm and may be so large as to occupy almost the entire abdomen. A characteristic x-ray finding on the plain films of the abdomen is a tapering ("bird's-beak") termination of the lower end of the area of colonic distention (Fig. 4-2). A barium enema will also demonstrate a tapering of the advancing end of the barium column (Fig. 4-5). Careful attention to the x-ray findings is extremely important. The differential diagnosis must be made between sigmoid volvulus and the other common types of left colon obstruction (i.e., carcinoma, diverticulitis, etc.) because the treatment is different for sigmoid volvulus.

The primary treatment of sigmoid volvulus is proctoscopic intubation of the sigmoid colon with a large (no. 36) rubber tube. Proctoscopy alone will often

decompress the colon. At the time of the emergency proctoscopy the mucosa of the bowel should be carefully inspected. If it is cyanotic or suggestive of ischemia or gangrene, emergency laparotomy is indicated. If an ischemic or gangrenous sigmoid volvulus is present, resection is indicated. Either a Hartmann or a Mikulicz procedure should be done. Closure of the stoma and reanastomosis can be performed at a later date after proper bowel preparation. If neither gangrene nor ischemia is present, the tube can often be inserted and passed upward into the sigmoid colon. Its position is maintained by suturing to the skin of the anus and tube. The tube should be left in place for 3 or 4 days and definitive resection rescheduled at a future date, probably during the same hospitalization because of the high incidence of recurrence.

Diverticulitis of colon. Diverticulitis of the colon is one of the common causes of colon obstruction, although much less common than primary colon carcinoma. There are many parallels between colon obstruction due to diverticulitis and that due to primary carcinoma. Most obstructions of the colon secondary to diverticulitis, similar to those due to carcinoma, occur on the left, i.e., the descending, sigmoid, and rectosigmoid areas. Obstructions occurring in other areas of the colon due to diverticulitis are rare.

The operative procedures indicated in colon obstruction caused by diverticulitis of the left colon are essentially the same as in colon obstruction caused by carcinoma. In colon obstructions due to diverticulitis[39] there are frequently clinical findings of an acute inflammatory process in the lower abdomen, suggesting the possibility of acute appendicitis with an accompanying ileus. Exteriorization cecostomy has the advantage of allowing adequate examination of the appendix to rule out this possibility. If right transverse colostomy is preferred, the lower abdomen should be carefully explored at laparotomy. In the rare cases of diverticulitis causing obstruction of the colon in areas other than the descending, sigmoid, or rectosigmoid areas, the same operative procedures are indicated as previously described for colon obstructions due to carcinoma. In some cases of colon obstruction due to diverticulitis there is a concurrent pericolic abscess, particularly in the lower left quadrant of the abdomen. If this situation is present, the abscess should be drained, preferably extraperitoneally through a left McBurney incision, at the same time that an exteriorization cecostomy or transverse colostomy is performed.

Extracolic pelvic carcinoma. Pelvic carcinoma, exclusive of colon carcinoma, is not an uncommon cause of obstruction of the pelvic colon (i.e., sigmoid and rectosigmoid), particularly in females. In addition to the usual x-ray and clinical findings of colon obstruction, a mass may be palpable in the pelvis by abdominal, vaginal, or rectal examination. This is a distressing situation and usually the prognosis is grave.

The extracolic carcinomas that cause such obstructions most often arise from the ovary (usually the left) or uterus and rarely from the fallopian tubes. These carcinomas may be primary or recurrent.

This type of colon obstruction should be treated either by a loop colostomy of the left colon or a Hartmann-type left colostomy. The stoma should be placed well proximal to the carcinomatous obstruction. If later radical gynecologic procedure or drug therapy proves to be curative, the stoma may then be closed. However, this desirable situation rarely occurs.

Postoperative adhesions. Postoperative adhesions are the most common cause of obstruction of the small intestine. Adhesions are a rare cause of obstruction of the colon. In the unusual cases of colon obstruction, lysis of the adhesions is the procedure of choice. In addition, a tube cecostomy should be done to decompress the colon.

Colocolic intussusception. Colocolic intussusception (Fig. 4-8) is a rare cause of colon obstruction. The common ileocecal type of intussusception is, in reality, a form of small bowel obstruction.

Colocolic intussusception is of two types: primary (idiopathic) and secondary (to a colon carcinoma, which is usually polypoid; to a benign polyp; or to an intramural benign colon neoplasm). Primary colocolic intussusception usually occurs in infants or small children. The etiology is not clear. The signs, symptoms,

Fig. 4-8. Colocolic intussusception.

and x-ray findings are essentially the same as in the common ileocolic intussusception.

Barium enema, in expert hands, can be an efficacious form of reduction of the intussusceptum. Immediate careful evaluation of the entire colon after reduction is indicated to rule out the possibility of a secondary intussusception. If barium enema is unsuccessful as a therapeutic measure, if there is a question of secondary intussusception, or if the diagnosis is in doubt, an immediate operation is indicated. If, at operation, a nonstrangulated primary colocolic intussusception is found, simple reduction is all that is necessary. Concurrent tube cecostomy is usually indicated for temporary decompression of the colon. If there are gangrenous changes in the bowel and the intussusception is located in the right or transverse colon, primary ileocolectomy is indicated. If the intussusception is gangrenous and located in the left colon, a Mikulicz- or Hartmann-type resection is indicated. The resulting stoma can be closed at a later date. If a secondary colocolic intussusception is present, immediate laparotomy is indicated. At operation the intussusception is first reduced. The involved colon is then examined through an adequate colotomy incision. If a benign lesion is found, it can be excised. A concurrent tube cecostomy should be done. If a malignancy (carcinoma or lymphoma) is found in the right or transverse colon, a primary ileocolectomy is the procedure of choice. If biopsy proves the presence of a malignant neoplasm (carcinoma or lymphoma) of the left colon, a Mikulicz procedure or Hartmann resection should be performed. The resulting stoma is closed at a later date.

Incarcerated external abdominal hernia. Incarcerated external abdominal hernia is a common cause of small bowel obstruction. This etiology is a rare cause of colon obstruction. When the colon is thus obstructed, inguinal hernias or large incisional hernias are the most common causes. When an inguinal hernia obstructs the colon, it occurs most often on the left side. The sigmoid colon is most often involved, and the hernia is usually of the sliding type.

In this situation, if the colon is not gangrenous, reduction and repair of the hernia will also remedy the obstruction. If the colon is markedly distended, a concurrent tube cecostomy is indicated. If the involved colon is gangrenous, a Mikulicz- or Hartmann-type resection is indicated. This procedure is best done through a second abdominal incision placed above the inguinal incision.

In right inguinal hernias the cecum may become obstructed. Repair of the hernia with restoration of the cecum to its intraperitoneal position will relieve the obstruction. Concurrent tube cecostomy should be done through a McBurney or small transverse incision placed above the inguinal incision. At the time of hernia repair, if a gangrenous cecum is present, a right ileocolectomy is indicated. This procedure is also best done through a second, more superiorly placed incision. Colonic obstruction sometimes occurs through a ventral hernia. Any part of the colon may be involved, although the transverse colon is the most frequent site of obstruction. In nonstrangulating obstructions of this type, repair of the hernia will relieve the obstruction. Concurrent tube cecostomy should also be done through a separate small McBurney or right transverse lower quadrant incision. Strangulated colon may be found in large incisional hernias. If the right or transverse colon is involved, an ileocolectomy with an ileotransverse colostomy is the procedure of choice. If the left colon is strangulated, a Mikulicz- or Hartmann-type resection is indicated.

Inflammatory gynecologic disease. Inflammatory gynecologic disease, particularly left tube ovarian abscess, can produce obstruction of the sigmoid or rectosigmoid colon. Surgical extirpation of the gynecologic disease will usually relieve the colon obstruction. Depending on the degree of colon distention, concurrent tube cecostomy may be indicated through a separate incision in the lower right quadrant.

Mesenteric artery thrombosis or embolus. Acute thrombosis or embolization of the mesenteric vessels is an unusual condition that causes acute vascular obstruction of the colon. When this occurs in the superior mesenteric artery, which supplies the right colon and small intestine, areas of the small intestine are also involved. Therefore this clinical syndrome is primarily one of ischemic small bowel obstruction and is not pertinent to this discussion. Arterial thrombosis, embolization, or occlusion of the inferior mesenteric artery (left colic artery, etc.) rarely produces ischemic changes in the left colon. The collateral circulation (from the superior mesenteric and middle hemorrhoidal arteries) is usually adequate to prevent ischemia of the left colon.

The inferior mesenteric artery (or left colic artery) is frequently sacrificed in the process of resection of abdominal aneurysms. Rarely does this cause ischemic changes in the left colon. However, occasionally ischemic changes will occur in the left colon because of inadequate collateral circulation of the inferior mesenteric artery. The clinical picture is bizarre. Ileus develops insidiously and is most often localized to the left colon. Proctoscopic examination usually shows ischemic changes in the lower sigmoid colon.

When such a situation is suspected, a barium enema should not be done because of the danger of perforation of the ischemic left colon. The treatment of choice is a Hartmann-type left colectomy. The rectal stump is sewn over and the left colon is resected. The proximal viable colon is brought out as a single-barreled colostomy. The colon and rectum can be anastomosed at a later operation.

Colonic obstruction secondary to herniation through foramen of Bochdalek. Isolated obstructions of the transverse colon or splenic flexure through the foramen of Bochdalek have been recorded in the literature. We have seen two such cases. It is interesting that the radiologic findings are indistinguishable from obstruction in the same area due to carcinoma.

Repair (transabdominal) of the hernia is the treatment of choice. This procedure will also relieve the colon obstruction. When strangulation is present, an ileocolectomy should be performed if the patient's general condition is good. In the poor-risk patient an exteriorization (Mikulicz) resection is the treatment of choice.

Ameboma. Ameboma of the colon is an uncommon cause of colon obstruction in this country. In South and Central America this lesion is quite common.

Obstruction of the colon due to ameboma is most common in the right colon, particularly in the ileocecal region. However, all parts of the colon can be affected. The clinical picture is somewhat similar to obstruction caused by carcinoma of the colon. In many cases there are prodromal or concurrent symptoms of amebic dysentery. Simultaneous perforation of the ameboma is not uncommon.

This condition can occur in any age group. Michel has observed such cases among infants and children in South America. These patients present poor

operative risks. Conservative surgical procedures are indicated. Rarely should primary ileocolectomy be done, even in the right colon. The procedure of choice is an exteriorization colectomy (Mikulicz). Biopsies, smears, and cultures for ameba should be taken in order to determine the exact diagnosis.

Prolapse of stoma. A stoma created by either single- or double-barreled colostomy may prolapse[13] and cause obstruction of the proximal colon. The diagnosis in such situations is evident without elaborate diagnostic procedures. A prolapsed stoma can often be reduced manually. However, in most cases operative revision or resection is indicated.

Intraperitoneal inflammatory disease (exclusive of gynecologic disease). Intraperitoneal inflammatory disease, other than gynecologic diseases or inflammatory processes of the colon, can produce the clinical picture of colon obstruction. This is particularly true of advanced acute or subacute cholecystitis, usually with localized perforation, or in advanced cases of acute appendicitis. In the former, there is a large inflammatory mass in the upper right quadrant of the abdomen that can involve the hepatic flexure of the colon. The resulting clinical picture may be difficult to distinguish from an intrinsic colon obstruction of the same area.

The treatment is surgical eradication of the biliary disease. This can be combined with a tube cecostomy if the colon distention is marked.

Complicated advanced appendicitis, usually with localized perforation, can produce the clinical picture of colon obstruction in the cecal or ileocecal region.

Duplication of colon. Duplication of the colon[14] is a rare and interesting lesion. Obstruction occurs most frequently in infants and children, but may become manifest at any age. The clinical pattern may be either slow and insidious, presenting as an incomplete or chronic obstruction, or an acute obstruction of the colon. In the former, elective colectomy is indicated after proper preparation. In the latter, the technique to be followed is essentially the same as described for primary colon carcinoma. In infants with isolated colon duplications, primary resection can usually be performed. In some cases the surgeon may choose to do an exteriorization Mikulicz procedure.

Irradiation colitis. If a patient has had extensive irradiation therapy of the pelvis for carcinoma, injury to the pelvic colon (rectosigmoid and sigmoid) may result. The colon becomes scarred and fibrotic. Stenosis and obstruction may result. The clinical picture in such cases is usually gradual and insidious. Acute obstruction may occur, but this is uncommon.

If the obstruction is gradual and insidious, elective colectomy, after proper preparation, is indicated if the carcinoma is considered to be cured. If the obstruction is relatively acute, the treatment is the same as described for carcinoma of the rectosigmoid and sigmoid colon. In some of these cases a high sigmoid colostomy may be adequate.

Rarely does obstruction of the colon, other than the rectum or rectosigmoid, result from extensive intra-abdominal irradiation. In such unusual cases the treatment is the same as for primary colon carcinoma.

Fecal impaction. High fecal impaction is a common cause of colon obstruction in immobilized patients, especially the elderly. The obstruction usually involves the rectum and sigmoid colon. Impaction is easily diagnosed on digital rectal examination. A large firm mass of feces can be felt by the examining finger.

The cure of fecal impaction simply involves manual removal of the feces. Occasionally anesthesia (general or spinal) is necessary in high, solid impactions.

OPERATIVE TECHNIQUES

The operative techniques used in the various operations for colon obstruction merit specific comment.

Exteriorization cecostomy. The procedure of exteriorization cecostomy should be performed through a short transverse right lower quadrant incision (Fig. 4-9). It is important to mobilize the cecum so that it can remain partially outside the abdominal wall without tension. Suturing of the cecum to the abdominal wall is usually not necessary if mobilization has been adequate. It is important that the ileocecal valve or terminal ileum not be obstructed in closure of the wound. In order to be certain of this, a slight rotation of the cecum to the left at the time of mobilization may be necessary. The wound is then closed around the exteriorized cecum as previously described. After the wound is closed, the exteriorized cecum is immediately decompressed by insertion of a trimmed no. 36 Pezzer catheter that is attached to a plastic bag. In 24 hr the catheter can be removed and the cecum opened widely in the patient's room without using anesthesia. Ligation of several small vessels may be necessary. Some surgeons prefer to open the cecum with a cautery because of the hemostatic effect.

In some cases of colon obstruction in which exteriorization cecostomy is intended, the cecum may be so distended and possibly ischemic that there is danger

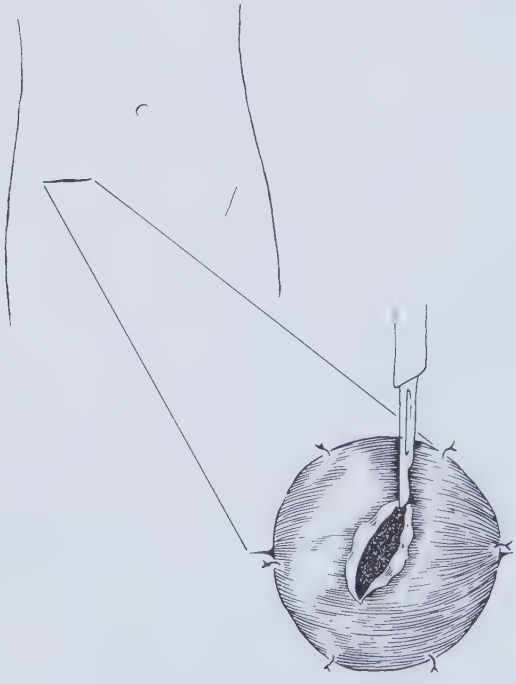

Fig. 4-9. Exteriorization cecostomy.

of perforation during mobilization and exteriorization. In such situations, tube decompression of the cecum should be done before mobilization is attempted. Many surgeons argue that the exteriorization cecostomy creates a greater risk of morbidity for the patient than simple tube cecostomy or right transverse colostomy and also that there may be excessive loss of fluid from the exteriorized colon. From the standpoint of morbidity, the patient has to tolerate the exteriorized cecum for only 10 to 14 days if the obstruction is due to carcinoma or 6 weeks if the obstruction is caused by diverticulitis. A large type or "stick-on" ileostomy or colostomy bag will usually handle the fecal outflow. The loss of fluids, electrolytes, and protein from the exteriorized cecum may be significant and must be managed by adequate replacement therapy.

One advantage of the exteriorization cecostomy is that at the secondary procedure (usually a left colectomy) it can be quickly changed to a tube cecostomy. The tube can be removed when the patient's lower bowel function has returned to normal. The majority of the resulting cecal fistulas will close spontaneously.

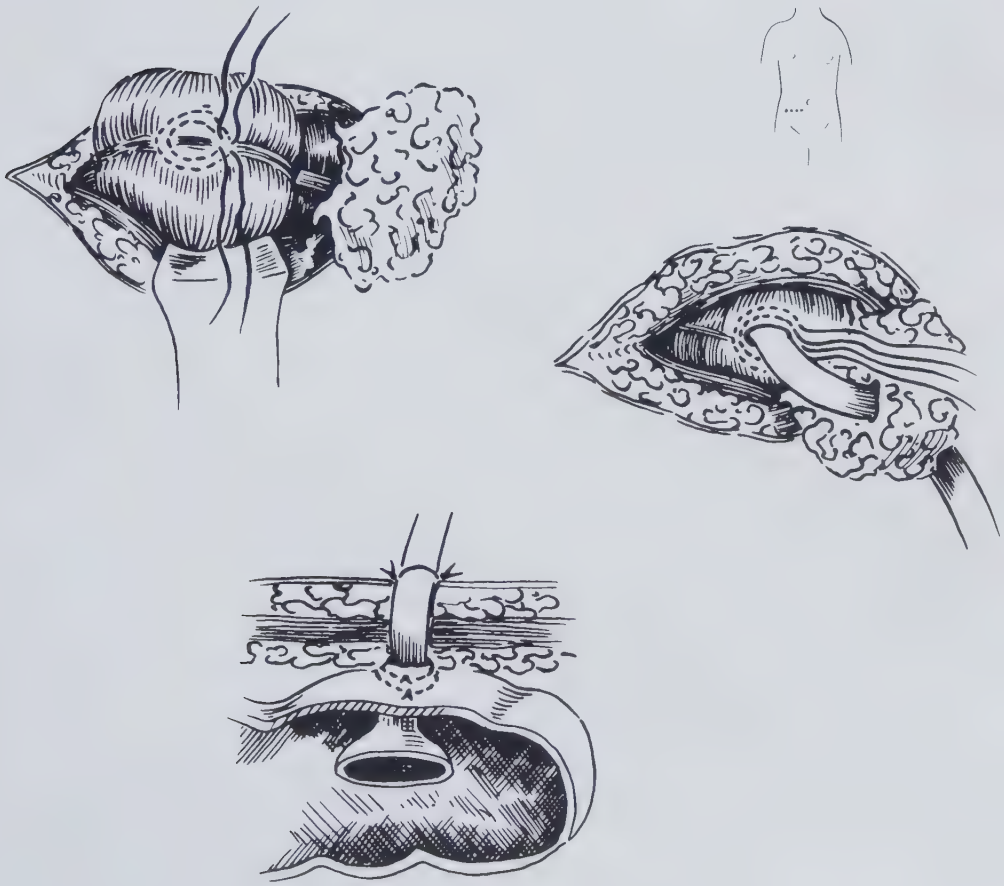

Fig. 4-10. Tube cecostomy.

The skin irritation resulting from exteriorization cecostomy may cause some problem. However, this can be remedied by frequent cleansing, a proper fitting ostomy bag, local skin care, and steroid ointments.

Tube cecostomy. Tube cecostomy (Fig. 4-10) is the most ancient of the procedures for decompression of the colon when obstruction is present.[2, 7, 19] It is rarely if ever indicated in obstructing diverticulitis or in perforated colon carcinoma. The degree of decompression and defunctionalization is inferior to that obtained when an exteriorization cecostomy or right transverse colostomy is performed. Tube cecostomy can be done under local anesthesia, particularly in elderly, poor-risk patients. We prefer a right transverse lower quadrant incision because this allows concurrent exploration of the abdomen. Some surgeons prefer a McBurney incision. The procedure should be done with a trimmed no. 36 Pezzer catheter. This is held in place with two or three purse-string sutures of atraumatic, chromic catgut. Reinforcing Lembert sutures of silk may also be used. The cecum must also be sutured to the abdominal wall.

When tube cecostomy is performed, the tube should be left in place for 4 to 5 days after the subsequent colectomy, by which time the patient's bowel function will have returned to normal. In some cases, depending on the location of the carcinoma, resection of the cecostomy can be done if an ileocolectomy is performed as the curative operation.

Right transverse colostomy. Right transverse colostomy[10, 11, 18, 38] is the procedure of choice of the majority of surgeons for the treatment of obstruction of the left colon (left transverse, descending, sigmoid, and rectosigmoid areas) caused by carcinoma or diverticulitis (Fig. 4-11). This procedure produces a high degree of immediate decompression and defunctionalization of the left colon.[36]

Right transverse colostomy should be performed through a short upper right quadrant transverse incision. After the incision is made, a loop of the right transverse colon is carefully delivered into the wound until it rests well outside the skin incision without tension. A Penrose drain is inserted through the mesocolon of the exteriorized loop and tied loosely over the loop. A short glass rod may also be used but we do not prefer it. The abdominal wall and skin is then closed snugly around the exteriorized loop with interrupted figure-of-eight plastic sutures. The stoma is opened immediately after the skin closure.

Primary colectomy. In good-risk patients with obstruction of the right or transverse colon or occasionally splenic flexure due to carcinoma, primarily ileocolectomy may also be considered. This procedure can also be done in the rare case of obstructing diverticulitis of the right or transverse colon.

Operative and postoperative decompression of the small intestine with the Leonard, Miller-Abbot, Cantor, or Baker tubes may be necessary if there is concurrent small bowel distention.

Exteriorization (Mikulicz colectomy). In rare situations an exteriorization (Mikulicz) type of colectomy may be indicated in colon obstructions. This procedure can be done through a midline, paramedian, or transverse incision. On entering the abdomen, the liver and regional lymph nodes are carefully examined for evidence of metastases. The portion of the colon to be mobilized is carefully dissected free by incising the peritoneal attachments and removing the omentum. Any part of the colon except the lower sigmoid area can be mo-

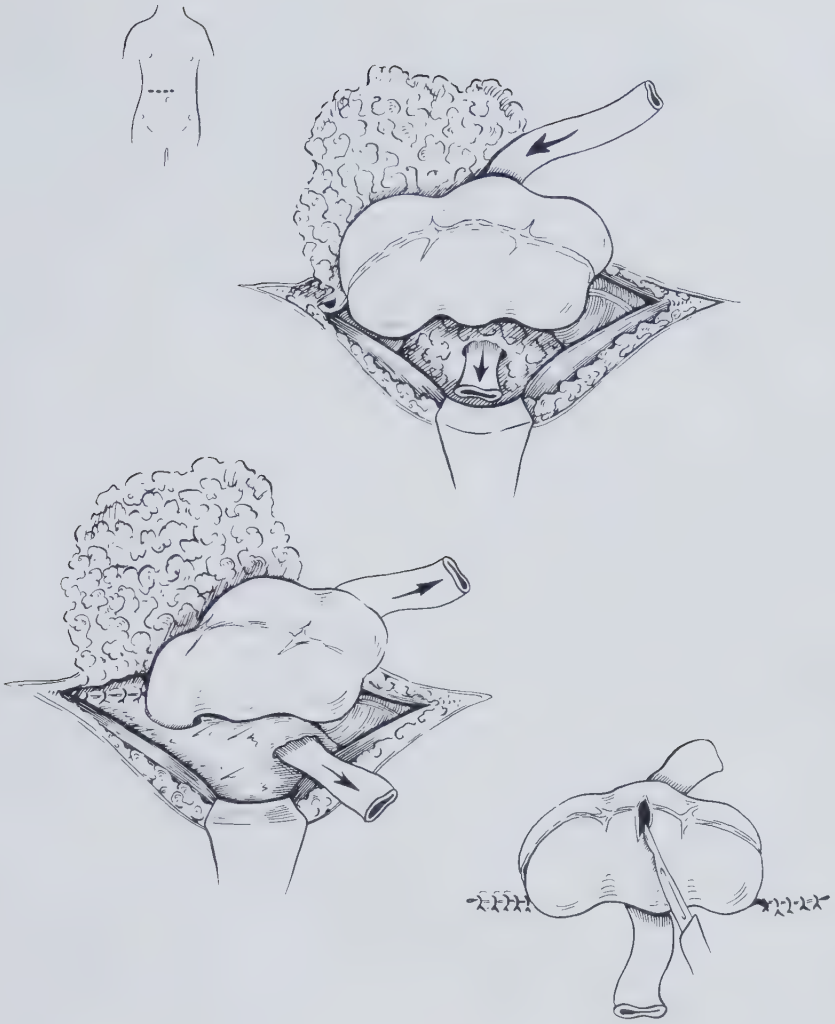

Fig. 4-11. Right transverse colostomy.

bilized to such an extent that it will lie well outside the abdominal wall without tension.

A Penrose drain is placed through the mesocolon beneath the apex of the loop to be exteriorized, and the involved loop can be drawn well outside all layers of the abdominal wall. Suturing to the abdominal wall is usually not necessary. The abdominal wall is closed primarily around the exteriorized loop with interrupted figure-of-eight plastic sutures. The loop of exteriorized colon is removed after the skin closure, either with the scalpel or by cautery. The stoma resulting from the double-barreled colostomy can be closed at a later date.

Hartmann left colectomy. The Hartmann left colectomy is most frequently indicated in gangrenous sigmoid volvulus. In such cases the gangrene frequently extends to the rectosigmoid area. As a result, a Mikulicz resection is not feasible.

In the Hartmann colectomy the rectosigmoid colon is transected below the gangrenous area. The distal end is closed over with a running inverting suture of 0 chromic atraumatic catgut reinforced with an inverting serosal layer of Lembert 3-0 silk sutures. The distal end of the colon is dropped back into the pelvis. The gangrenous colon above the rectosigmoid is then rapidly resected upward until an area of viability is reached. At this point the colon is transected between Payr's clamps, and the gangrenous colon is removed. Extensive dissection of the mesentery is not necessary.

The resulting proximal stoma is brought out through the original incision (midline or left paramedian) or, preferably, through a small stab wound lateral to the incision. At a later date the proximal colon can be mobilized and anastomosed to the rectosigmoid colon.

Ileotransverse colostomy. Occasionally in carcinoma obstructions of the cecum, ascending colon, and hepatic flexure, because of the poor condition of the patient, it may be best to perform an ileotransverse colostomy and defer resection to a later date when the patient's general condition improves. The procedure is best done through a midline or right paramedian incision. A transverse incision may also be used.

In performing the ileotransverse colostomy, the ileum should be transected 20 to 25 cm from the ileocecal valve. The proximal cut end of the ileum is anastomosed to the side of the transverse colon. The distal cut end of the ileum should be brought out through a McBurney stab wound in the lower right quadrant. A trimmed Pezzer or whistle-tipped catheter (no. 34 to no. 36) should be passed through the terminal part of the ileum into the cecum in order to obtain immediate decompression thereof. This is particularly important if the ileocecal valve is competent.

The catheter is fixed to the distal free end of the ileum with two or more purse-string sutures of 00 chromic atraumatic catgut or silk. One or more of these sutures should pass through one side of the catheter in order to assure fixation of the catheter, the end of which is in the cecum. The catheter can be removed in several days or can be left in place until the later resection is performed.

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5

Procurement and preservation of kidneys for transplantation

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The number of lives that could be saved by human cadaver kidney transplantations has been limited by the supply of suitable organs. Estimates of the number of people in the United States each year who could benefit from kidney transplantations range as high as 10,000 to 30,000. The primary source of limitations is the relatively small percentage of people dying under suitable circumstances who are even considered for organ donation. The estimated 2500 transplants that were performed last year must represent only a small fraction of the kidneys made available by the 57,000 fatal automobile accident victims. In efforts to increase the yield, many transplantation groups are asking surgical colleagues in other hospitals, even at some distance, to assist in the harvest and preservation of organs. Consequently, it has seemed appropriate to include a brief presentation of the background, current techniques, and future trends of this area in a book concerned with current practices in surgery.

By far the majority of organs being used at this time are kidneys, although eyes have been banked for some time and the use of cadaver skin is increasing in burn units. Use of other tissues must still be considered experimental and will not be discussed in this chapter.

BACKGROUND

The earliest efforts in organ preservation were attempts to recreate an artificial body environment with a pump (heart) and some sort of oxygenator (lung). Interest ran high in the scientific community and spilled over to the lay public. Charles Lindbergh designed and built one of the first organ perfusion systems with the advice of Alexis Carrel. However, these experiments with

perfusates, including whole blood, at normothermic body temperature had unsatisfactory results primarily because the technical inadequacy of the equipment and conduit did not allow atraumatic flow of the perfusate. Lysis of cellular elements and denaturation of proteins occurred quickly. Even today with modern perfusion pumps and tubing, shear forces on red blood cells do not allow prolonged perfusion, and investigators have uniformly turned to cell-free perfusates. Again, however, these sophisticated perfusion solutions will allow only short-term normothermic preservation, up to about 90 min.

The next problem with normothermic perfusions is the generation of the toxic products of metabolism of the organ and their accumulation in the closed perfusion system. It becomes necessary to provide a detoxification system such as a liver. Then perhaps the whole thing should be regulated by a system of endocrine glands, and soon the additions have turned the system into an entire body. This approach has been proposed by Dupree et al.[24] who "stored" organs for several days by transplanting them experimentally into heavily irradiated primates.

The successful storage of whole blood at cold temperatures and perhaps the successful freezing of bull semen for storage spurred investigators in organ preservation to study the possibility of cold storage of organs. The object, of course, was to drastically lower the rate of metabolism and prevent the accumulation of toxic products. However, hypothermia brought its own collection of problems. It soon became apparent that rapid uniform cooling was desirable and could be best accomplished by intra-arterial perfusion of a precooled solution. Cooling of human plasma results in precipitation of certain lipoproteins and other debris that plug the capillary system of a perfused organ. These materials are removed to a great extent by freezing and thawing plasma, followed by filtration through microfilters to produce "cryoprecipitated" plasma.

It has been suggested that lowering the rate of metabolism in the cold lowers the efficiency of the cellular cationic pump, allowing sodium ions and water to enter cells and to produce swelling and damage to the organ.[69] The swelling produced by long-term continuous perfusion of cold saline solutions has been countered by three means. First, such perfusions should be short, only long enough for the core temperature of the organ to reach that of the perfusate. In human kidneys under arterial perfusion this only requires 3 to 5 min. Second, Collins et al.[19] have suggested that the ionic composition of the solution should mimic intracellular ions rather than extracellular concentrations and that most of the sodium ions should be replaced with potassium and magnesium ions. Finally, it has been pointed out that if the perfusion pressure is raised for only a fragment of a perfusion cycle, as in a pulsatile perfusion system, swelling does not occur. These three means underlie most of the widely used techniques for kidney preservation in use today. The excised organs are given a brief hypothermic flush with Collins' solution or Ringer's lactate supplemented with additives, stored in ice, and, if storage of over 8 hr is contemplated, placed on one of the pulsatile perfusion machines.

The techniques in use need further refinement because results are not uniformly satisfactory. There seem to be two main patterns of injury. First, because of improper preparation of the donor or rough handling of the organ during its excision, vasospasm may be induced in the fine arterial vascular supply. This

vasospasm has proved very difficult to reverse. Recently addition of phentolamine to the perfusate has shown some benefit,[45] but other drugs have been ineffective. Current techniques emphasize prevention rather than cure.

The other injury pattern is the lysosomal membrane lysis induced by a variety of injuries, particularly hypoxia. Instability of these membranes allows the egress of autolytic enzymes into the cell sap and the perfusate. Accumulation of lactic dehydrogenase, beta glucuronidase, cathepsin D, and similar substance in perfusates can be shown to be correlated with organ injury. Avoidance of hypoxia and of swings in pH of the perfusate help to prevent lysis. Certain agents such as methylprednisolone[65] and phenothiazines have the ability to stabilize lysosomal membranes.

The entire field of tissue freezing used successfully for the storage of blood up to 4 years has yet to yield fruit for the storage of organs. The problem seems related to difficulties in obtaining uniform rates of freezing and thawing throughout the organ. The problems of ice crystal artifacts and sequestration of ions within cells in concentrations sufficient to denature membrane lipoproteins have been solved to a great extent in systems where cells are dispersed or in a thin membrane such as skin. Here temperatures are uniform throughout the system, and cryoprotective agents such as glycerol, dimethyl sulfoxide, or microdextrans added to the medium control these two injury mechanisms. Application of these techniques to whole organs has not given satisfactory results as yet.

MORAL AND LEGAL ASPECTS

The major religions in the United States have voiced no opposition to the performance of transplantation procedures. Indeed there has been little difference between the members of the Catholic, Jewish, and Protestant religions with regard to the willingness to donate organs after death. Although the acquisition of organs from dead individuals has a somewhat unattractive flavor, the public has generally accepted this mode of therapy as a good and reasonable method of medical treatment. A Gallup poll taken in January, 1968 indicated that 70% of the population would be willing to donate kidneys after their death. A willingness to donate organs was associated with a higher educational status. The concept of cadaver organ transplantation has in general been well accepted by the public, but the decision to donate a deceased relative's part in any specific instance is met with a higher degree of reservation. Typically the acceptable donor is a young individual who is the victim of an accident and whose death is unexpected and a severe shock to the family. The old and debilitated whose death is somewhat expected are usually not acceptable donors. The forcefulness with which physicians should pursue the permission necessary to perform organ harvesting remains in a gray area with no well-defined procedural guidelines. Indeed a major concern of some has been the possible exploitation of poor and less well-educated persons who might be pressured into donating. Every effort must be made to avoid exerting undue pressure and to ensure that the donation is of the relatives' own free will.

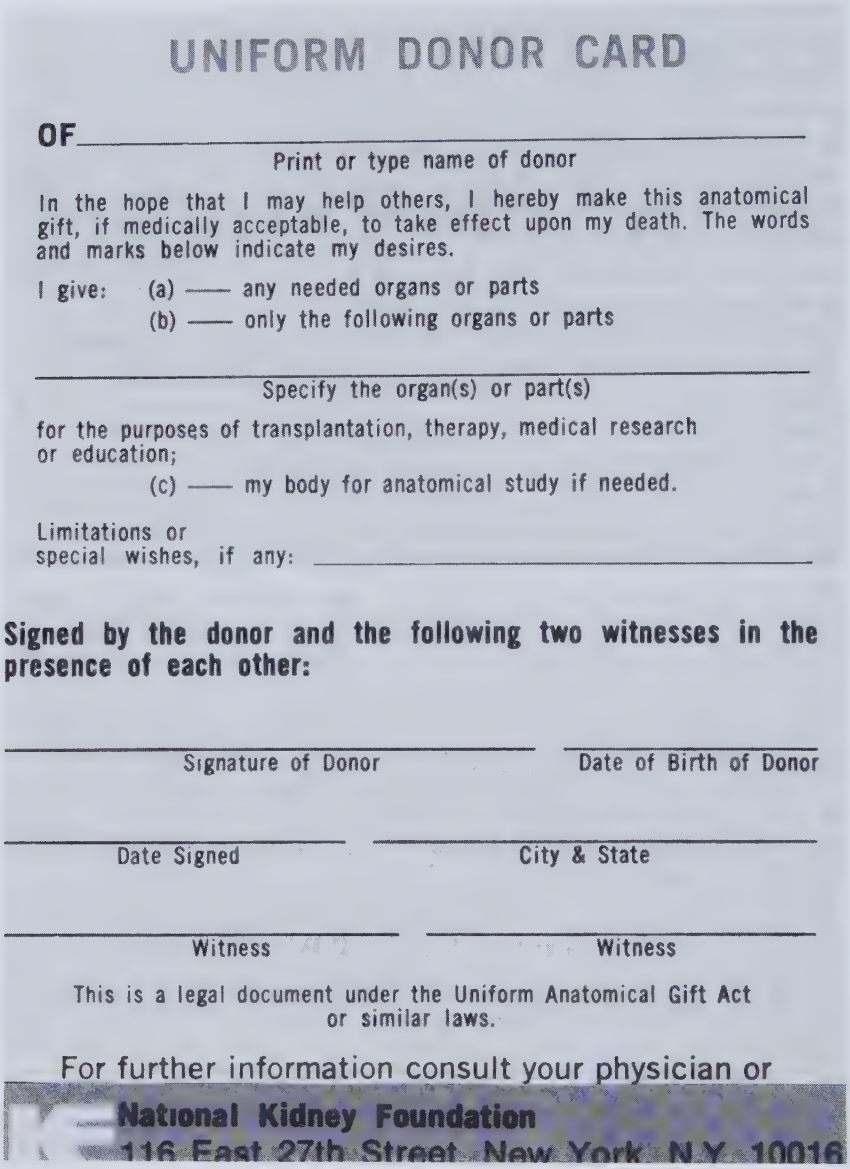
The problems of defining death, the amount of treatment to be given to the hopelessly incurable, and the traditional charge to the physician to preserve life and relieve suffering have become entangled in an ethical quagmire by the

rapid advancement of the medical sciences.[5, 41] Lawyers, clergyman, lay individuals, legislators, and physicians have all become deeply involved in an attempt to answer some of the questions that arise. The legal implications of organ harvesting cover several areas. The first involves determination of when death has occurred, for no organ can be harvested prior to this time in a cadaver-type situation. Second, proper authorization must be obtained, usually from relatives and in accident cases also from the coroner. Third, it appears reasonable and necessary for the organ transplantation team to be divorced from any care of the potential donor prior to his demise. Finally, no form of remuneration is offered to the relatives who give permission for the donation.

Although in this country it is well accepted that permission must be obtained prior to organ removal, this is not necessarily the case in other countries. In Sweden, France, and Israel the state has permission to remove organs without family permission unless the donor had expressly opposed such a procedure while he was alive.[63] In Virginia it is possible for the medical examiner to provide consent for organ donation if the next of kin are unable to be notified and if the family has no known objection. Usually permission is obtained from the surviving spouse, parent, child, or next in line of relationship. It is essential that the particulars be well explained, particularly the fact that it is preferable to remove the organs while the cardiorespiratory system is being supported and the heart is actively beating. It is recommended that the written permission explicitly state this condition. This does not rule out the use of a donor whose heart has ceased beating if, in the judgment of the harvesting surgeon, the organs might be resuscitated. It is advisable for the physician to speak primarily with the individual responsible for giving permission. Other interested parties cannot, despite their assistance or hindrance, make the decision for donation. It is significantly easier to explain the necessary facts to an individual than to a "committee" of relatives.

The Uniform Anatomical Gift Act written by the Governors' Commission on Uniform Legislation with the assistance of several sources of medical and clerical advice has now been passed with slight modification by all of the 50 United States.[50] The act provides significant improvement in facilitating the acquisition of organs for transplantation.[21, 56, 57] There are several important aspects to this act.

1. It permits an individual to donate all or part of his body prior to death.
2. It authorizes an autopsy examination to ensure medical acceptability of the gift when donation has been agreed to.
3. It permits next of kin to donate the organs or body of their relatives at the time of death.
4. It provides for the use of donor cards carried on the person to act as legal wills not requiring probate.
5. It does not define the time or circumstances of death, but allows the determination to rest with the physician in charge of the donor's case.
6. It specifically separates the physician caring for the donor prior to death from those physicians harvesting the organ.
7. It protects all persons acting in good faith in accordance with the terms of the act from liable damages or prosecution in criminal proceedings.



UNIFORM DONOR CARD

OF_____
Print or type name of donor

In the hope that I may help others, I hereby make this anatomical gift, if medically acceptable, to take effect upon my death. The words and marks below indicate my desires.

I give: (a) —— any needed organs or parts
(b) —— only the following organs or parts

_____
Specify the organ(s) or part(s)

for the purposes of transplantation, therapy, medical research or education;
(c) —— my body for anatomical study if needed.

Limitations or special wishes, if any: _____

Signed by the donor and the following two witnesses in the presence of each other:

_____ _____
Signature of Donor Date of Birth of Donor

_____ _____
Date Signed City & State

_____ _____
Witness Witness

This is a legal document under the Uniform Anatomical Gift Act or similar laws.

For further information consult your physician or
National Kidney Foundation
116 East 27th Street New York N.Y. 10016

Fig. 5-1. Both sides of uniform donor card.

The definition of death has recently been discussed by many individuals and study groups. Simply, death occurs when the patient's attending physician says it occurs. The diagnosis is left to the physician in most circumstances and has, by tradition, been accepted as the time when spontaneous respiration and heart function cease. However, because it now is possible to resuscitate individuals after cardiorespiratory function has ceased, this definition of death has recently been opened to question. The Kansas and Maryland legislatures have codified the Harvard Ad Hoc Committee recommendations into a law pro-

viding *one* set of criteria of death. This type of legislation has been both applauded and condemned.[36]

The concept of brain death is helpful for the procurement of the best prepared organs for transplantation. The Harvard Medical School Ad Hoc Committee to examine the definition of brain death proposed the following criteria[22]: (1) unreceptivity and unresponsiveness to externally applied stimuli and inner needs, (2) absence of spontaneous respirations and movements, (3) no elicitable reflexes, and (4) flat electroencephalogram (EEG). It was suggested that these findings be verified 24 hr later and that there be no evidence of hypothermia or central nervous system depressant administration.

A general review of the criteria of death has been undertaken by the Task Force on Death and Dying of the Institute of Society Ethics and the Life Sciences.[71] The Harvard criteria that include the use of EEG tests showing no activity 24 hr apart may be unduly strict. Some feel that the persistence of spinal cord reflexes should not preclude the diagnosis of cerebral death.[75] Other measurable parameters that have been suggested as a definition of death include stagnation in the carotid siphon or the absence of cerebral blood flow on angiography (intracranial cerebral blood flow ceases when intracranial pressure equals 67% of the arterial pressure). The availability of consultants who can evaluate neurologic death is important. It is the patient's personal physician, however, who must determine the time of expiration. The first court test of "cerebral death" has resulted in a favorable verdict for the physicians who proceeded with a heart transplantation on the basis of cerebral death.

It has been estimated that 10.8% of all patients coming to autopsy are possibly acceptable as kidney donors.[53] Others using stricter criteria calculated that 0.6% of the people dying in an urban population would be suitable for renal donation.[26] Couch[20] has estimated that 4000 to 5000 donors should become available each year in the United States. To obtain these organs for transplantation requires a concerted effort not only on the part of the transplant surgeon but also on the part of the medical community, particularly neurosurgeons and neurologists, as well as the general public. Considerable effort has been expended to develop programs for cadaver organ harvesting, and the use of donor cards (Fig. 5-1) has been promoted to facilitate donation and to publicize the need for cadaver organs. A donor card when signed in the presence of two witnesses is a legal document. To nullify the intention to donate, one merely destroys the card.

DONOR EVALUATION AND PREPARATION

Living donors involve primarily those individuals offering kidneys or skin for transplantation. The evaluation of potential living kidney transplant donors is usually performed in transplantation centers. The evaluation of these individuals is detailed and complete in order to ensure excellent bilateral renal function and the absence of any diseases that would compromise the donor or the transplant recipient. Cadaver kidneys, however, may be harvested in any hospital where a potential cadaver donor becomes available. In some situations the cadaver donor is transported to the transplant center for evaluation and kidney harvesting. In most circumstances, however, kidney harvesting takes place at the local hospital. It is here that surgeons in the community can take

an active part in procuring, harvesting, and transporting viable kidneys.

The increased need for cadaver kidneys has resulted in a greater demand to harvest all available organs and, consequently, the requirement that surgeons other than those involved primarily with transplantation be available to obtain these organs. It is open to question as to when the harvesting team should become involved with evaluating or advising in the care of a potential transplant donor. Obviously no member of the harvesting team should become involved with the primary care of the patient prior to the determination of death. Nor should there be involvement when the decision as to when death occurred. Nevertheless, practical considerations demand that decisions to maintain organ viability must often be made prior to the actual pronouncement of death and to this end suggestions by the harvesting team are most helpful. There is general agreement by most individuals doing transplantation as to the criteria for determining the suitability of cadaver kidneys to be used for transplantation. Every effort is expended to use every available kidney. Where borderline situations occur, harvesting the organs and evaluating their perfusion characteristics may be a practical means for determining viability. Each situation must be analyzed in its own right, and each final decision regarding the use of cadaver kidneys for transplantation will depend on the exigencies of the situation.

Evaluation

The general criteria for a suitable renal cadaver donor specify individuals 50 to 55 years of age or younger, no history of malignancy (other than of the central nervous system), no infectious diseases, no known chronic renal disease or hypertension, satisfactory renal function at the time of harvesting, the ability to obtain appropriate permission, and the potential availability of the kidneys within ½ to 1 hr after cessation of renal blood flow (warm ischemia). The criteria have varied across the country. Some centers demand a heart-beating cadaver before kidney harvesting. Others have accepted the presence of hypotension, the use of vasopressors, and the presence of anuria within 24 hr of the time of donor nephrectomy.[9]

The typical circumstances surrounding a renal cadaver donor usually involve a young healthy adult who has been involved in an accident and has sustained irreparable brain damage. Other conditions that have led to a suitable cadaver donor have included central nervous system tumors, postoperative craniotomy, postoperative cardiac surgery and cardiac injury, subarachnoid hemorrhage, ruptured cerebral artery aneurysm, drug overdose, massive trauma, pulmonary embolus, and myocardial infarction. By far the most common condition is severe head trauma, usually secondary to an automobile accident. Kidneys harvested from patients with hepatorenal syndrome have been used successfully in renal transplantation operations.[38]

The two most important factors in determining the immediate posttransplant function of a cadaver kidney are the condition of the donor prior to nephrectomy and the length of the warm ischemia time at the time of nephrectomy. These factors are more significant than the type of storage during the interval between nephrectomy and reimplantation of the kidney in the recipient. The criteria we employ in evaluating potential cadaver renal donors may be found in the following list.

Cadaver donor criteria

Diagnosis of death established
Authorization (family, coroner, or medical examiner)
Systemic diseases excluded:
  Hypertension
  Chronic renal disease
  Diabetes
  Collagen disease
  Generalized atherosclerosis
Malignancy excluded (other than central nervous system and "cured" cancers)
Infections excluded:
  Septicemia
  Abscesses
  Hepatitis
  Genitourinary infections
  Peritonitis
Age $<$ 55 years
Renal function satisfactory
Hypotension $<$ 12 hr
Warm ischemia $<$ 1 hr

Diagnosis of death. The determination of death must be established prior to the procurement of any organs for transplantation. The decision as to when death has occurred must be made by physicians not associated with the transplantation procedure. Neurosurgical or neurologic consultation is to be encouraged, and a diagnosis by a consensus of several physicians is most desirable.

The criteria for establishing brain death vary among physicians and institutions. Usually the patients suffer from cerebral trauma, vascular lesions, or central nervous system tumors. Other causes of unresponsiveness such as hypothermia, metabolic derangements, and depressant drug administration should be ruled out. There should be deep coma without response to external stimuli and no deep tendon reflexes, spontaneous movements, or pupillary reflexes. The absence of spontaneous respirations is documented for 3 min after removal from the respirator. The patient must have a satisfactory P_{CO_2} and have been breathing room air for 10 min prior to the trial. Additional criteria of cerebral death that have been suggested include negative caloric tests, an isoelectric EEG (two are often done 24 hr apart), and the absence of cerebral blood flow demonstrated by arteriographic studies.

Authorization. Permission from the individuals who will be responsible for the remains of the deceased must be obtained prior to harvesting. Usually this involves the next of kin, but it can involve friends who will be responsible for the burial if there are no living relatives. In accident cases it is essential to notify the coroner or medical examiner and gain approval for organ harvesting. In some states the coroner may give permission to harvest organs when the relatives cannot be reached or there is no known opposition to the organ harvesting either by the patient prior to his death or by the next of kin. Coroner permission is not provided for in the Uniform Anatomical Gift Act. Homicide cases have been generally avoided because of the potential legal complications. However, the increased demand for cadaver kidneys is creating pressure on physicians to use donors who have died under suspicious circumstances.

It is essential that autopsy permission be obtained to enable a thorough

examination to rule out systemic diseases that might adversely influence the use of the donor kidney in a transplantation operation. In addition, it is important to make clear the need for obtaining tissues other than the kidneys, such as portions of the spleen or lymph nodes, to facilitate tissue typing. The Uniform Anatomical Gift Act specifies that permission for using organs for transplantation implies the authorization to remove whatever tissues and perform whatever examinations are necessary to safely and satisfactorily complete the transplant procedure.

Systemic disease. A variety of systemic illnesses can adversely affect renal function, and if present, they often preclude the use of organs for transplantation. Hypertension, chronic renal disease, diabetes, and collagen disease are generally considered to be contraindications to harvesting kidneys for transplantation. Evidence of generalized atherosclerosis is a relative contraindication. The presence of subarachnoid hemorrhage from berry aneurysms is associated with an increased incidence of polycystic disease of the kidneys. This can be identified at the time of nephrectomy and does not in itself preclude an attempt at kidney harvesting.

In each of these conditions, judgments must be made as to the severity of the condition. Mild cases of diabetes of adult onset that require only some mild dietary management should probably not be a contraindication to donor nephrectomy. Similarly a mild unsubstantiated history of hypertension must be examined critically before ruling out the possible cadaver donor kidney.

Malignancy. Patients dying of carcinoma or lymphoma are unacceptable as cadaver donors. This is because of the well-documented risk of transplanting tumors with the renal allograft.[61] Brain tumors do not usually metastasize outside the central nervous system, and individuals dying from this type of tumor are acceptable as cadaver donors. Carcinomas of the head and neck and soft tissue sarcomas metastasize to the kidney in at least 5% and 10% of cases, respectively.[49] Patients with superficial epidermoid carcinomas of the skin and basal cell carcinomas of the skin are probably acceptable as transplant donors if there is no evidence of metastatic spread of the tumor. More difficult to evaluate is the suitability of a patient who has had a tumor but who has been apparently cured for several years. A definite recommendation cannot be made; however, people with tumor-free intervals of 3 to 5 years after treatment are probably suitable as donors. A transplanted tumor has an unpredictable course and may persist or regress after discontinuation of immunosuppressive therapy and removal of the transplanted kidney. Most often, satisfactory results have been obtained with disappearance of the tumor.

Infectious disease. Individuals with generalized infections and/or septicemia are excluded from donating. Peritonitis, abscesses, and fulminant pneumonia are absolute contraindications. However, individuals with positive urine cultures and even pneumonia have at times been used as renal transplant donors. If the kidneys cannot be removed without being contaminated, they should not be used. Patients with syphilis, malaria, and hepatitis should be excluded. Liver function tests and Australia antigen examinations of the serum can help in excluding patients with hepatitis. Caution should be exercised in evaluating the fevers commonly associated with trauma to the central nervous system. Typically these are not infectious in origin and are the result of the central nervous sys-

tem injury per se. Chest x-ray examinations will be helpful to exclude those patients with pulmonary complications.

Age. The age of the donor is probably not significant with respect to the final function of the donated kidney provided the warm ischemia time is not unduly prolonged. Sells and Pena[62] found that kidneys from donors over 50 years of age with warm ischemia times equal to the times in younger age groups had no appreciable increase in the average duration of transplant oliguria, whereas when the warm ischemia time was prolonged there was an increased duration of transplant oliguria in the older donors. The use of newborn kidneys is still considered experimental, with early thrombosis occurring in these kidneys.[9] It appears necessary to transplant both kidneys if the donor is a young child and the recipient is an adult. Otherwise the kidneys may be used separately in transplantation into children of comparable size.

Renal function. It is difficult to define absolute indications and contraindications to kidney donations with respect to the various degrees of renal function. Urine output of at least 50 ml/hr is desirable. Normal serum creatinine, blood urea nitrogen, and creatinine clearance are good indications that there will be prompt, early, and satisfactory renal function after transplantation. However, because of the desperate need for cadaver kidneys and because kidneys that do not have normal function prior to harvesting will often ultimately function satisfactorily after a period of acute tubular necrosis, some transplant surgeons are accepting donors that are oliguric for 24 hr or more as long as the donor serum creatinine is less than 3 mg%. Others feel that 12 hr of oliguria is the maximum allowable. Usually young healthy individuals who have no history of renal disease are acceptable candidates provided they have only a slow terminal deterioration of renal function that is compatible with the patient's hypotension and dehydrated state. In these donors a serum creatinine level of 3 mg% as suggested by Belzer et al.[12] is probably a good cutoff point. Evaluation of the blood urea nitrogen must take into consideration the use of urea to treat cerebral edema, which may elevate the blood urea nitrogen and give a false impression of decreased renal function. Also, diabetes insipidus following head injuries can result in marked dehydration and subsequent decrease of renal function. The inability to respond to a potent diuretic such as furosemide or ethacrynic acid is an indication to some transplant surgeons to reject a potential cadaver donor.

Hypotension. Hypotension in itself is not a contraindication to kidney harvesting. The renal function that is manifested by the hourly urine output is much more critical in evaluating the patient. A low blood pressure in the face of adequate urine production is not a rejecting feature. When hypotension is associated with decreased renal function and neither can be improved by fluid or drug administration, it is generally felt that kidneys under these circumstances are not suitable for harvesting. Usually hypotension for over 12 hr that is unresponsive to treatment and is associated with a decrease in renal function is a valid contraindication to cadaver kidney harvesting.

Ischemia. Warm ischemia of over 1 hr generally results in a kidney being unsuitable for transplantation, and kidneys undergoing 2 hr of warm ischemia should never be used.[78] Times of 30 min or less are much preferred. Indeed several reports have indicated that warm ischemia beyond 15 min showed a

significant and definite increase in the incidence of postoperative anuria. Short warm ischemia times may permit kidneys to be stored without perfusion for considerable periods of time. Alhough some have used human kidneys successfully after a hypothermic flush and 15 hr of storage in ice,[15] we have preferred to limit storage to 8 hr.

Tests. The laboratory examinations necessary for evaluating potential renal cadaver donors are limited to a few basic procedures that should be readily available in most circumstances. A routine urinalysis and microscopic examination is necessary. The creatinine clearance on a 1 or 2 hr sample with a Foley catheter in place is most helpful. A urine culture should be obtained for reference in the treatment of the recipient after transplantation. Blood tests include serum creatinine, blood urea nitrogen, electrolytes, liver function, and Australia antigen screening tests. The latter can usually be performed within several hours in many blood banks and is helpful to exclude some patients with hepatitis. Tissue typing can be performed on a peripheral blood specimen prior to the time of donor nephrectomy; however, difficulties are often encountered in accurate tissue typing cadaver donors with peripheral blood. Consequently, we have preferred to delay tissue typing until a lymph node specimen is obtained at the time of donor nephrectomy. A large enough pool of potential cadaver transplant recipients should be available so that regardless of the tissue type, suitable candidates can be found to receive the kidneys. Blood cultures can be obtained if there is a febrile episode, but usually a decision as to whether this is neurologic should be made prior to harvesting the kidneys. Under special circumstances an intravenous pyelogram may be useful, particularly in the event of abdominal trauma. Usually, however, organ harvesting will proceed, and an estimation of any renal trauma can be made at the time of operation. Chest x-ray examination can rule out pneumonia as a cause of fever. We store a sample of serum and lymphocytes in the freezer for retrospective studies.

Preparation

The procedural steps necessary in harvesting cadaver organs are involved in large part with organization, communication, and timing. A large number of individuals are involved with cadaver organ harvesting, and excellent coordination is absolutely essential for a smoothly functioning operation. A single individual must take command and be responsible for ensuring that all the details are attended to. This responsibility usually rests with the senior surgeon or his delegated representative. An efficiently functioning unit that has harvested many kidneys will usually have a well-defined plan already established. Those institutions where only an occasional organ harvesting occurs would benefit from procedural guidelines worked out well in advance. The exact method of proceeding will vary from institution to institution and with different medical personnel. A general approach to the problem, however, is helpful and a series of steps such as those listed in the protocol on p. 125 can be formulated that will be of assistance.

The particulars involved in the diagnosis and time of death have been discussed previously. It is essential, however, to stress the need for a proper entry in the patient's record by the physician and/or consultants who have ascertained that the patient has died. Prior to the patient's death, overtures to the family

PROTOCOL: CADAVER ORGAN HARVESTING

1. Diagnosis and time of death entered in the record by the physician and/or consultant
2. Permission obtained for organ removal (kidney, eye, skin, pancreas, liver, pituitary gland, intestine, lymph node, and other), autopsy examination, and lymph node excision
3. Symbolic last viewing of the body by the family and consideration of religious requirements
4. Coroner permission obtained in accident and other selected cases
5. Organ harvesting team and transplantation center alerted; includes surgeons, anesthesiologists, tissue typing technicians, and organ perfusion technicians
6. Administrative personnel notified to assist with procedural regulations, financial matters, and organ transportation
7. Cardiorespiratory support established:
   a. Ventrilator (100% O_2 and portable apparatus for transport to operating room)
   b. IV fluids
   c. Vasopressors
   d. Vasopressin for antidiuretic hormone insufficiency
8. Criteria for suitable donor fulfilled (See outline p. 121.)
9. Diuretics to maintain diuresis
   a. Furosemide
   b. Ethacrynic acid
   c. Mannitol
10. Phenoxybenzamine, 1.0 to 1.3 mg/kg IV ½ to 1 hr prior to nephrtctomy
11. Methylprednisolone, 1000 mg IV 1 hr prior to nephrectomy
12. Immunosuppression of donor (cyclophosphamide, 3 Gm) 12 hr prior to nephrectomy (optional)
13. Cold (4° C) perfusion solution (Collins', Ringer's lactate or saline solution) prepared and shipping containers with donor information forms available

are usually made, and a general understanding of their agreement to organ donation is obtained. When the final written permission is received, the physicians should remember the need for other organs and tissues used in clinical and experimental transplantation and for the extraction of hormones (pituitary gland). Often the family requests to view the remains of the deceased for the last time. Any special religious requirements should be respected. In all accident cases and other selected instances, permission from the coroner is essential.

After these initial steps in obtaining permission have been completed, the organ harvesting team is contacted and the operating room alerted. If the organ harvesting is not taking place at a transplantation center, then the center is notified of the potential availability of organs for transplantation. Surgeons, anesthesiologists, and technicians involved with tissue typing and organ perfusion are told of the family's decision to donate the organs. Administrative personnel are contacted in order to assist with procedural regulations, financial matters, and transportation of the organs. Cardiorespiratory assistance is maintained with the use of a ventilator, and arrangements are made for portable

ventilatory assistance devices in order to transport the patient to the operating room. Intravenous fluids are administered, depending on the central venous pressure, the blood pressure, and the urine output. Vasopressors are given if indicated to maintain the blood pressure. Caution is exercised, however, in order to prevent vasospasm in the kidney secondary to these drugs. Antidiuretic hormone insufficiency in association with head injuries may often require vasopressin (Pitressin) for control of the diabetes insipidus. If intravenous fluid administration is used alone to treat this disorder, massive pulmonary edema may supervene.

The donor is examined, all laboratory data reviewed, and a decision as to the suitability for organ donation is determined. (See list on p. 121.) At times a delay in making a decision may be necessary in order to evaluate the cadaver's response to various measures such as intravenous fluid administration and diuretic therapy. If there is some question as to the suitability of the donor, there should be no hesitancy in consulting with the transplantation center. Usually diuretics are administered to ensure a brisk diuresis. The urine output is replaced usually with dextrose, 5%, in 0.5N saline solution. After ensuring that the blood volume is normal, phenoxybenzamine, an alpha adrenergic blocker, is administered intravenously in doses of 1.0 to 1.3 mg/kg, ½ to 1 hr prior to nephrectomy. This prevents vasospasm and therefore ischemia in the harvested kidney. Methylprednisolone, 1000 mg, is given intravenously 1 or 2 hr prior to organ harvesting.[46] The use of immunosuppressive drugs (cyclophosphamide, 3 Gm intravenously) given to the donor 12 hr prior to nephrectomy is optional but has been reported to improve long-term kidney function.[27] The solution that will be used to wash out the kidneys must be prepared ahead of time and cooled to 4° C. In addition, the shipping containers with donor information forms must be available for immediate use.

OPERATION

The function of a cadaver kidney after transplantation is clearly related to the physiologic status of the organ in the cadaver at the time of removal, but it is also surprisingly sensitive to the technical aspects of its removal. The rough handling of a kidney with subsequent vasospasm increases the likelihood of posttransplantation acute tubular necrosis. A short ureter or vein complicates the technical aspects of completing the various anastomoses in the recipient. Although one surgeon is adequate in harvesting kidneys, two surgeons certainly facilitate matters not only with regard to the technical aspects of the nephrectomies but also with regard to assisting with the hypothermic flushing procedures, placing the organs in containers for shipment, and the completion of forms. When the cadaver is "brain dead" but has an intact circulatory and ventilatory system, the dissection to remove the kidneys can be performed deliberately and without haste. This is obviously preferable to the situation where the donor dies suddenly, and the kidneys must be removed more rapidly in order to minimize the warm ischemia time. Total body heparinization, external mechanical cardiac massage, and peritoneal hypothermia[74] have all been used to advantage under these circumstances. A procedure for cadaver nephrectomy is outlined on p. 127.

PROCEDURE OF CADAVER NEPHRECTOMY

1. Sudden death—cardiac asystole
   a. 15,000 units heparin IV and cardiac massage
   b. Remove kidneys in <1 hr (preferably <30 min)
   c. Occasionally done at bedside
2. Brain death cadaver
   a. Phenoxybenzamine, 1.0 to 1.3 mg/kg given 1 hr prior to nephrectomy, or chlorpromazine, 1.0 to 1.3 mg/kg IV 1 hr prior to nephrectomy
   b. Maintain renal function (fluids, diuretics)
   c. Methylprednisolone, 1 Gm IV 2 hr prior to nephrectomy
   d. Operating room procedure
3. Sterile preparation of abdomen
4. Midline incision with bilateral supraumbilical transverse extensions
5. Hemostasis ("brain dead" cadavers)
6. Heparin, 15,000 units 5 min prior to nephrectomy
7. Methods:
   a. En bloc resection of both kidneys
   b. Individual nephrectomies
8. Objectives:
   a. Maximal length of vessels and ureter
   b. Preservation of periureteral soft tissue
   c. Identify multiple vessels
   d. Minimal warm ischemia time
9. Immediate hypothermic washout of kidneys:
   a. Collins' solution
   b. Ringer's lactate
   c. Saline solution
10. Lymph node excision for tissue typing
11. Exploration of abdomen and biopsy of suspicious lesions (tumors)
12. Closure of abdomen
13. Completion of forms
14. Letter to relatives and physicians

Anatomy

There are several anatomic features in the performance of a cadaver nephrectomy that deserve emphasis. Multiple renal arteries occur in 25% of kidneys.[13] When multiple, there are usually only two arteries involved, but on occasion three or more vessels may be present. It is essential that this arterial variation be identified, as the renal arteries are end arteries without intraparenchymal anastomoses, and ligation results in infarction of a portion of the kidney. Early division of the main renal artery may occur close to its origin, and present the same hazards as multiple renal arteries. These anomalies can often be managed by taking a Carrel patch from the side of the aorta that encompasses all the arterial orifices. A variety of additional techniques can also be used to circumvent the problem of multiple renal arteries. We have frequently joined two arteries in a side-to-side fashion to form a single common lumen. End-of-artery to

side–of–renal artery anastomosis as well as the use of branches of the hypogastric artery are some of the additional methods that have been suggested. Small arteries to the upper poles that are too small for anastomosis may be ligated without complications except for a small infarct. However, small tributaries to the lower pole also provide significant vascularization of the ureter and renal pelvis and are sacrificed only with some trepidation.[68]

Venous anomalies are common, especially on the right side. Small accessory veins may be ligated with impunity because of the extensive intrarenal venous anastomosis. Even large veins can be sacrificed so that a single venous anastomosis may be performed. It is important to ligate the ovarian, spermatic, and adrenal veins that drain into the left renal vein. Additional venous tributaries to the renal veins, including lumbar veins, are variable and must be identified and ligated. Small cortical vessels are not important except that they must be ligated to prevent bleeding when blood flow to the kidney is reestablished in the recipient. Duplications of the urinary collecting system do occur and require identification for proper handling. Double implantations into the bladder are usually performed to circumvent this problem. The renal artery is best visualized from the posterior aspect with the kidney elevated and mobilized anteriorly and medially. A heavy neuroplexus around the origin of each artery can make dissection in this area difficult and result in inadvertent incisions into the aorta.

Important features

There are several features of the kidney harvesting operation that are important. Obviously whenever possible two kidneys are harvested. A gentle atraumatic dissection is essential to prevent renal artery vasospasm and the subsequent vascular insufficiency that will result following reinstitution of the blood flow. In order to circumvent this problem, it has been suggested that the renal hilus be infiltrated with local anesthesia around the renal vascular pedicle. The efficacy of this procedure has not been documented. It is important to obtain a maximal length of renal vein and artery. This can be ensured by the en bloc dissection of both kidneys with the aorta and the inferior vena cava. Otherwise a cuff of aorta or inferior vena cava can be removed with each of the respective vessels.

A satisfactory length of ureter with an abundance of surrounding soft tissue is essential. An adequate length of ureter is usually obtained by dividing at or below the pelvic brim. Dissection in the renal hilus is limited in order not to compromise the ureteral blood supply. It is important not to skeletonize the ureter in order to preserve an adequate vascularization. Ligation of all vascular tributaries will prevent significant leaks while on pulsatile perfusion or when vascular blood flow is reestablished in the recipient. After the kidneys have been removed, visual inspection with perhaps frozen section biopsies should reveal any gross abnormalities and permit a decision with regard to the kidney's suitability for transplantation. In most institutions the maximal allowable warm ischemia time has been 1 hr, with some stating that 2 hr of warm ischemia should never be exceeded.[16] Fifteen minutes of warm ischemia appears to be the dividing line between those kidneys with immediate function and those having a high incidence of acute tubular necrosis postoperatively.

Procedure

Surgeons who are experienced in organ procurement methods are best qualified to remove cadaver kidneys. Inexperience in harvesting kidneys has resulted in damage to the ureter and the renal vessels and stripping of the renal capsule. Some injuries are sufficient enough to exclude kidneys from being transplanted. Future needs for large numbers of cadaver organs, however, will demand the participation of surgeons in the community to harvest the organs that become available. Therefore surgeons must be trained in the specific techniques of kidney harvesting in order to obtain satisfactory organs for transplantation.

A variety of harvesting routines are available. One that has proved satisfactory in our experience is outlined on p. 125. Patients who die suddenly with cardiac asystole are immediately given 15,000 units of heparin solution intravenously, and cardiac massage is instituted to circulate the heparin and prevent thrombosis of the vascular system. Cardiac massage and assisted ventilation are continued until the kidneys are removed. The patient is quickly taken to the operating room for the bilateral nephrectomy to be performed or, in some instances, the procedure is carried out at the patient's bedside. The latter procedure is facilitated by the availability of a cadaver donor nephrectomy kit that is presterilized and contains the necessary gowns, drapes, instruments, and suture material. The kidneys must be removed within 1 hr of the time that circulatory function ceased. Preferably the kidneys should be perfused with cold solution within 30 min.

In those cadavers pronounced dead on the basis of absence of cerebral activity, bilateral nephrectomy can be planned and executed with more deliberation. Alpha adrenergic blocking agents, phenoxybenzamine, 1.0 to 1.3 mg/kg, and chlorpromazine, 1.0 to 1.3 mg/kg, are being evaluated at our institution and one of these drugs is given 1 hr prior to the anticipated time of nephrectomy. It is important to have a satisfactory blood volume at the time of phenoxybenzamine administration or there may be marked hypotension. Phenoxybenzamine and chlorpromazine have been helpful in preventing the renal vasospasm commonly associated with cadaver organ procurement. Adequate renal function is maintained with the use of fluids and diuretics. With the aid of portable respiratory assistance equipment, the patient is transported to the operating room where the nephrectomies are performed.

When time is available the abdomen is shaved; in any circumstance, it is prepared with an antiseptic solution and the procedure carried out under sterile conditions. A midline incision from the xiphoid to the symphysis pubis is carried into the peritoneal cavity. Bilateral supraumbilical transverse extensions of this incision may be needed to facilitate exposure of both kidneys. With "brain dead" cadavers, satisfactory hemostasis is obtained. The exact method of exposure and dissection will vary with the exigencies of the situation and the preferences and experience of the surgeon. In any case it is essential that 15,000 units of heparin be given 5 to 10 min before occluding the vascular supply to either kidney. In cases where the donor has died suddenly, the heparin will have already been administered.

An en bloc resection of both kidneys with the contiguous sections of the inferior vena cava and aorta can be performed expeditiously within 15 min (Fig. 5-2). This method is preferred when there are two small kidneys from a child

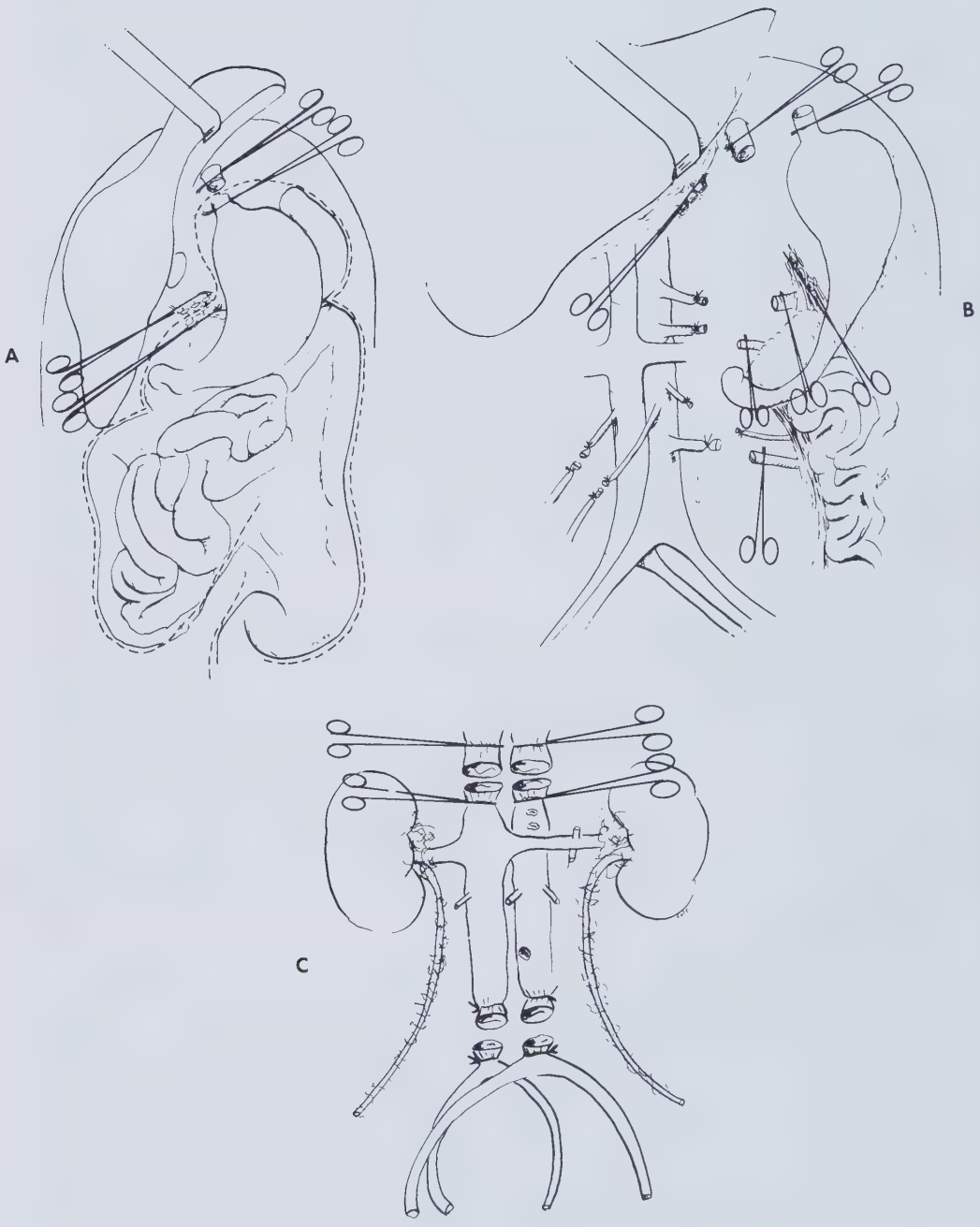


Fig. 5-2. **A,** Line of incision along peritoneal reflexions used to expose retroperitoneal viscera. **B,** Porta hepatis and esophagus are divided, and by anterior and medial traction on the stomach, pancreas, and intestines, the celiac axis and superior mesenteric and inferior mesenteric arteries are exposed and divided. **C,** En bloc resection of both kidneys and adjoining portions of aorta and inferior vena cava. Ureters are divided at pelvic brim.

that must be transplanted together into an adult in order to assure significant renal mass. The dissection is commenced by incising along the route of the small bowel mesentery around the cecum up along the lateral aspect of the ascending colon and second duodenum. The porta hepatis is divided between clamps and the gastrohepatic ligament divided up to the esophageal hiatus. The esophagus is then transected between clamps and the dissection carried downward, dividing the splenophrenic ligament. The splenic flexure of the colon and the descending colon are mobilized medially. The base of the sigmoid mesocolon is divided on both sides. With the visera then mobilized medially and inferiorly, the celiac axis, superior mesenteric artery, inferior mesenteric artery, and gonadal arteries are serially ligated and divided. This then effectively permits mobilization of the entire gastrointestinal tract, spleen, and pancreas inferiorly, exposing the entire retroperitoneal region. The inferior vena cava and aorta are then divided between ligatures below the renal vessels. With these vessels mobilized superiorly, their lumbar tributaries are secured and divided. The kidneys are mobilized from the surrounding soft tissue and the ureters divided distally at the pelvic brim. Once this is completed, the suprarenal aorta and inferior vena cava are both divided at the level of the diaphragm. The specimen is then removed and quickly perfused with cold washout solution. Metal clips can be used to facilitate occlusion of the vessels originating from the anterior aspect of the aorta and lumbar vessels. It is not essential to divide the esophagus, and some prefer not to divide it because of the possibility of bacterial contamination from the gastrointestinal tract.

Removing each kidney individually is probably more commonly practiced and can be equally satisfactory. However, more careful inspection and identification of renal blood vessels must be carried out using this approach. The right kidney is exposed by dividing the peritoneum along the line of Toldt and reflecting the right colon, duodenum, and head of the pancreas medially. The ureter is identified, and care taken during dissection to preserve an adequate amount of soft tissue around it. The ureter is then divided at the pelvic brim. With blunt and sharp dissection, the renal vein and artery are identified, and both are divided after completely freeing the kidney so that it can be removed and perfused at once. Often it is necessary to place curved vascular clamps proximal to the origin of the renal artery and the insertion of the renal vein in order to take a cuff of vascular tissue with each vessel. When there are multiple renal arteries, this maneuver greatly facilitates an anastomosis of the vessels via an onlay patch graft of the recipient's iliac artery. Infiltration of the renal vascular pedicle with 5 ml of 1% lidocaine may prevent vasospasm. The left kidney is then exposed by incising the line of Toldt along the descending colon and reflecting the hepatic flexure and descending colon medially. The left kidney is identified by incising Gerota's fascia, and a plane superficial to the renal capsule is developed with the use of blunt and sharp dissection. Cortical tributary vessels are ligated as they are encountered. As the dissection is carried medially, the immediate hilar area is avoided and the dissection of the vessels commenced in the soft tissue 2 cm from the renal hilus. This will avoid injury to small tributary blood vessels and to the vascular supply to the ureter. The adrenal vein entering superiorly and the ovarian or spermatic vein entering inferiorly into the left renal vein are both ligated and divided. Additional tributaries, which occasionally include the lumbar veins, will also require ligation and division. Identification of the renal artery or

arteries is made, and if a single renal artery is encountered, it is simply ligated and divided followed by ligation and division of the vein. If there are multiple arteries or a single renal artery is unduly small, a cuff of aorta encompassing the orifice(s) is removed from the side of the aorta. The left renal vein is long enough not to cause difficulty. Prior to clamping of the vessels the ureter is dissected, with particular care taken to preserving its adventitial soft tissue and avoiding compromising its blood supply. The ureter is divided distally at the pelvic brim. Each kidney after removal is quickly perfused with cold solution.

Despite the differences in technical methods of kidney removal, the objectives remain the same. These are to obtain the maximal length of artery, vein, and ureter, to preserve the periureteral soft tissues and not skeletonize the ureter, to identify multiple arteries when present and deal with them effectively, and to minimize the warm ischemia time. It is important to have the hypothermic washout fluid and small instruments necessary to cannulate the renal arterial lumen immediately available in the operating room. A variety of solutions have been proposed but are basically of two types—the intracellular type of solution such as Collins' solution and the extracellular type of solution such as Ringer's lactate or normal saline solution with heparin, procaine, albumin, glucose, and other ingredients added. The efficacy of these solutions is discussed in a later section of this chapter.

Prior to closure of the abdomen, it is essential that lymph nodes be obtained either from the small bowel mesentery or retroperitoneal regions for the purpose of tissue typing. These lymph nodes are sent with the kidneys to the hospital where tissue typing and lymphocyte cross-match procedures can be performed. Exploration of the abdomen to detect unsuspected conditions such as the presence of tumors is always important. Biopsies of suspicious lesions should be taken and submitted for frozen section examination. After the abdomen is closed, a member of the transplant harvesting team should be delegated to complete the appropriate forms and to write letters of appreciation to the relatives who have given permission for the procedure and the physicians who cared for the donor.

HYPOTHERMIC WASHOUT AND TRANSPORTATION

Flushing the cadaver kidney immediately on removal with a cold electrolyte solution is standard procedure in almost all transplantation centers. This immediately lowers the core temperature of the kidney and keeps the warm ischemia time to a minimum. The various ischemia times are important in evaluating and predicting the potential function of the harvested organs. The warm ischemia time begins with cessation of blood flow through the kidney (either when cardiac function ceases or, in the case of heart-beating cadavers, when the renal vasculature is occluded) and ends when the kidney is washed out with a cold perfusate. Cold ischemia time includes that period from the time the kidney is cooled until the kidney is removed from the cold storage phase and reimplantation is started. Some describe a *relative* warm ischemia time as the period when the kidney is exposed during reimplantation. More often this last division has been included in the cold ischemia period. The warming that occurs during the 15 to 30 min required to reconstitute the renal blood flow is minimal. The *pulsatile perfusion time* and the *total ischemia time* are self-explanatory.

Warm ischemia is most injurious to the kidney. It is estimated that 1 min of warm ischemia at 37° C is equivalent to 19 min of ischemia at 0° C, which corresponds to the twentyfold reduction of oxygen consumption by cadaver kidneys perfused at 5° C.[28, 40, 62]

Purpose

Perfusing the kidney with cold electrolyte solution fulfills two well-defined objectives. First, it immediately cools the entire kidney, decreasing the renal metabolic rate and limiting the warm ischemia time. Second, it flushes the kidney of donor blood, preventing thrombosis and eliminating lymphocytes and their associated antigens. Although surface cooling of kidneys removed from heparinized cadavers has been used alone as a primary means of decreasing the core temperature,[70] this method cools more slowly and obviously does not flush the kidney of donor blood. Many washout methods have not been demonstrated to be better than blood. Albumin Ringer's lactate and invert sugar used in human kidney washouts have been shown to be less desirable than blood left in the kidney.[19] Kidneys may be immersed in cold saline solution when the initial cooling flush is being carried out.

Other benefits of hypothermic washout are not as clearly defined. Elimination of an osmolar or electrolyte gradient, stabilization of cell and lysosomal membranes, and prevention of vasospasm have been suggested to be improvements resulting from the addition of a variety of ingredients to the basic electrolyte solution.

Solutions

Basically two types of cell washout solutions are used. One has an electrolyte composition similar to extracellular fluids and is usually based on Ringer's lactate or normal saline solution. The other is similar to intracellular fluid, as Collins' solution. To each of these solutions is added a variety of drugs and products; some of these have defined theoretic advantages; others do not. Additives have included albumin, glucose, fructose, mannitol, dextran, sodium bicarbonate, chlorpromazine, phenoxybenzamine, phentolamine, steroids, procaine, magnesium, heparin, papaverine, furosemide,[51] and antibiotics. The benefits of most of these additives are based on empiric observations. The large number of variables in the cadaver donor makes the analysis of washout methods difficult, and the experimental findings in the canine model are not necessarily applicable to man.

Other perfusates that have been used to cool the kidney have included diluted blood solutions,[39] plasma, and gas,[58] but presently these are not used with any frequency for hypothermic washout. These perfusates are less available and do not appear to have any advantage over the easily accessible salt solutions; indeed the gas perfusates have been uniformly unsuccessful. The chemical composition of the two representative solutions (intracellular and extracellular) are depicted in Table 5-1. The table does not list all the various washout solutions in use because of the almost unlimited number of permutations and combinations possible. The main controversy with regard to washout solutions concerns which of the solutions (intracellular or extracellular) is better. When the warm and total ischemia times are short, and the kidneys are harvested from a well-prepared

Table 5-1. Hypothermic washout solutions

Electrolyte composition	Extracellular (Ringer's lactate) (mEq/L)	Intracellular (Collins' C-4) (mEq/L)
Sodium	130	10
Potassium	4	115
Chloride	109	15
Magnesium	—	60
Bicarbonate	—	10
Sulfate	—	60
Phosphate	—	100
Lactate	28	—
Calcium	3	—
Additives		
Heparin		Papaverine
Dextrose		Steroids
Procaine		Antibiotics
Phenoxybenzamine		Insulin
Fructose		Furosemide
Mannitol		Chlorpromazine
Dextran		Phentolamine
Albumin		

cadaver, the type of washout solution with its various additives is probably of little importance in determining the quality of the transplanted kidney. When the warm and/or total ischemia times are long, the values of various flushing solutions become more controversial and are discussed later in this chapter.

The advantage of an intracellular solution seems to be its ability to eliminate an electrolyte gradient across the cell membrane. The addition of glucose or mannitol stabilizes the oncotic pressure and prevents cellular swelling. Kidneys perfused with saline solution lose potassium and magnesium. This loss can be minimized by perfusing the kidneys with solutions containing these ions in high concentration.[35] Our own experience indicates that intracellular solutions are better than extracellular solutions for the initial perfusion and cooling of the cadaver kidney.

Method

Cold perfusion of the harvested cadaver kidney should occur immediately after occlusion of the renal vasculature or as soon after the cessation of circulation as possible. In the cerebrally dead cadaver the vascular supply must not be divided until the kidney has been completely mobilized and the ureter divided; otherwise additional dissection after clamping the renal vessels will be required, which prolongs unnecessarily the warm ischemia time. The excised kidney is quickly placed in a basin that may be filled with iced saline solution. The renal artery(ies) is cannulated, with care being taken to avoid air in the perfusion line and thus an embolus to the kidney. When there are multiple arteries, provisions for cannulation and perfusion of several vessels at the same time should be made. The perfusate at refrigerator temperature is run into

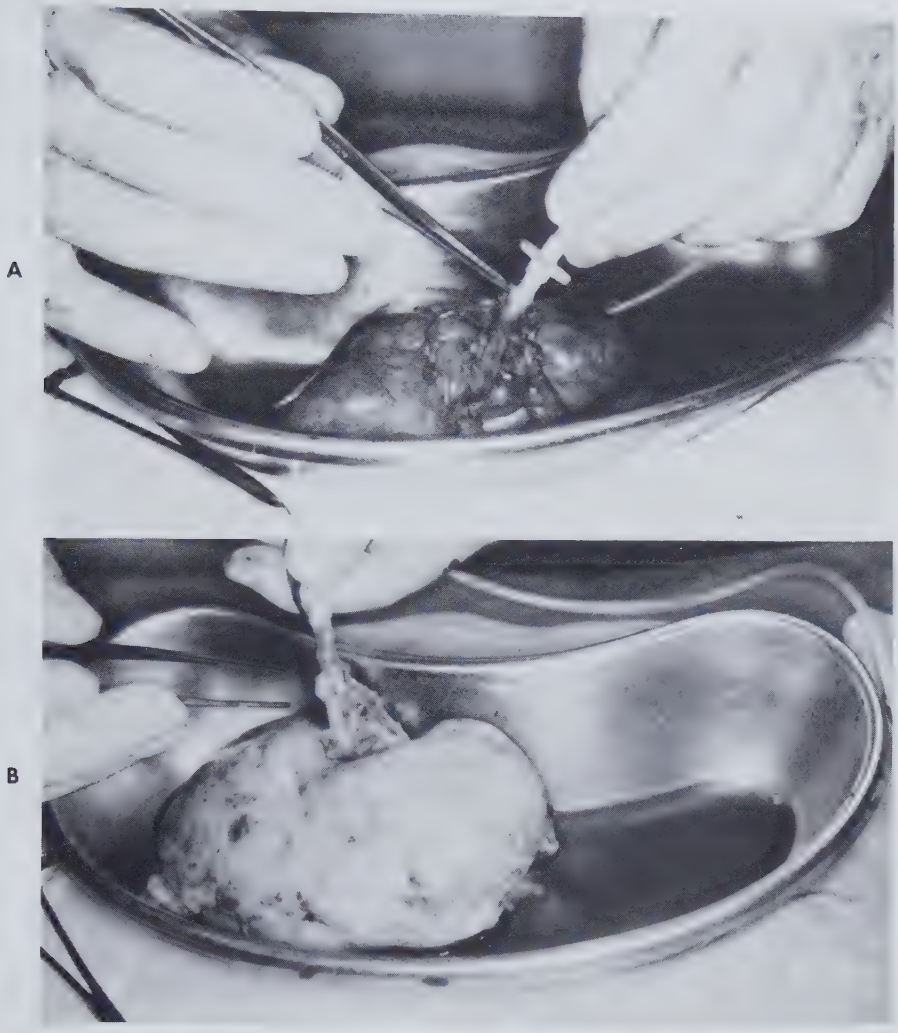


Fig. 5-3. A, Cadaver kidney prior to washout is dark and suffused with blood. **B,** Cadaver kidney after hypothermic washout is pale and cleared of blood.

the kidney from a height of 1 M, which approximately equals the mean arterial pressure. Careful attention is paid to the ease of perfusion. The rate of flow and the time needed to clear the renal vein effluent of blood are indicators of the degree of vasospasm present in the kidney. There should be a marked change in color from a dark hue indicative of an organ suffused with blood to a pale washed-out appearance (Fig. 5-3). The perfusion lasts for 3 to 5 min or until the venous effluent is clear, and usually 100 to 150 ml of solution is administered. Perfusion at higher pressures and for longer periods of time with large quantities of perfusate can be associated with renal interstitial edema. A satisfactory kidney pales uniformly and quickly within a few minutes. There is a fast flow and no mottling of the renal cortex. Poorly perfused kidneys are mottled with low flow rates and persistent blood in the venous effluent. If the washout charac-

teristics are poor, a decision must be made with regard to the kidney's suitability for transplantation. A trial of hypothermic continuous pulsatile perfusion may be instituted to monitor flow and perfusion pressure characteristics in an attempt to identify improvement.

Once the washout is completed, the kidney is prepared for transportation to the hospital where the transplant will be performed, or the kidney may be placed on a continuous pulsatile perfusion apparatus.

Transportation

Methods of storing kidneys during transportation between hospitals have ranged from simply placing the kidney in a cold solution surrounded by ice and packed in an insulated container to elaborate measures of maintaining continuous hypothermic perfusion by semiportable devices that must be carried in a truck or by smaller units that can be hand carried. Dramatic demonstrations of transporting kidneys for thousands of miles have emphasized the various prejudices of those advocating a variety of storage methods used to transport kidneys. Nevertheless, these demonstrations do emphasize the ability and the need to supply organs at a distance from the harvesting location.

Cooperation and sharing of kidneys between transplant centers have been increasing.[25, 54, 70, 73] The basic need for the sharing of kidneys is twofold. Most important is the need to ensure that every available kidney is used and that none are wasted. Because of ABO incompatibilities, there is a disproportionate number of potential recipients with blood group O as compared to patients with other blood groups awaiting renal transplantation.[73] As a result, 83% of transplant centers are not able to use both kidneys when an AB donor becomes available, and, with a type B donor, 28% of centers would be unable to use both kidneys. Of secondary importance is the attempt to find the best histocompatibility match on the basis of tissue typing.[52] The initial enthusiasm for tissue typing as the means of selection for successful cadaver transplantation has been tempered by failure to demonstrate close correlation of typing results and clinical results.[72] There are significant basic problems that remain to be solved before tissue typing is a determinant factor in human cadaver renal transplantation.[37, 44]

A national transplant communications network is functioning with over 2000 potential recipients with their tissue and blood types and antibody levels listed on a master printout.[73] This has helped select suitable recipients when cadaver kidneys cannot be used locally; moreover, it has facilitated finding identical histocompatibility antigen matches with cadaver donors. More data are needed to determine the benefit of identical matching in cadaver transplants.

Kidneys are shipped in a sterile polypropylene jar partially filled with cold electrolyte solution and surrounded by two plastic bags; the entire ensemble is enclosed in a Styrofoam container packed with ice. This packing can keep the kidney in good condition for at least 8 hr. A wide variety of containers have been used for this purpose. During packaging for shipment, it is essential to enclose a lymph node for tissue typing. Information about the ischemia times, the washout solution employed, the cause of death, the circumstances of harvesting (cardiac or brain death), the preparation of the donor (steroids, diuretics, phenoxybenzamine, etc.), and autopsy results should be recorded and sent with the kidney.

ORGAN STORAGE

In renal transplantation involving living donor organs the problem of organ storage is not of great importance. The operations are elective, with organizational and logistic problems solved in advance. The timing of donor nephrectomy and organ implantation in the recipient can be planned to minimize the avascular period, and cooling the kidney during the transition period will result in immediate function in the majority of cases.

The situation with cadaver donors is entirely different. Time is required to perform a variety of tasks, some of which can be completed only after the organ is harvested. A well-organized harvesting-transplant effort will do much to conserve time and effort, but it is usually impossible to completely synchronize these procedures. The ability to store organs is a real and practical aspect of cadaver organ transplantation.

Some of the benefits accruing to stored organs deserve mention. Preservation of viable kidneys permits transportation of kidneys between centers, allows accurate tissue typing on donor kidney cells or lymph nodes obtained at laparotomy, and provides time to dialyze and prepare the recipient for surgery. Postmortem examinations can be performed to search out malignancies and other systemic diseases that might adversely affect the transplant and/or the recipient. Operations can be performed on an elective basis when the surgical team is functioning optimally. The ability to test organ viability and perhaps to reverse vasospasm may be advantages of continuous hypothermic pulsatile perfusion.

Long-term organ preservation for weeks or years has not yet been realized. Human kidneys have been stored by pulsatile perfusion for 72 hr with functional recovery after transplantation.[76] Similar 72 hr results in dogs have been reported after hypothermic washout with an intracellular hyperosmolar solution containing mannitol followed by surface cooling.[55] The establishment of tissue and organ banks would permit the selection of appropriately matched organs to be transplanted in an elective manner when the recipient has been optimally prepared. This does not seem possible in the near future. We must for the present be content with the ability to routinely store kidneys for 24 hr and occasionally as long as 72 hr.

Several factors bear significantly on interpreting the results of various methods of organ preservation. Slapak[61] has outlined five damaging intervals in cadaver kidney transplantation. Severe damage during any of these periods will influence the organ's eventual functional recovery in the host. The first period involves the preagonal and agonal damage caused by hypotension, abnormalities in intravascular coagulation, acidosis, endotoxin release, and other factors in the immediate period prior to harvesting the kidneys or before cardiac activity ceases. In the second period, defined as the warm ischemic interval, anaerobic metabolism ensues with the production of lactic acid and the loss of cellular membrane integrity. The third interval includes the damage induced by the trauma related to the surgical excision of the organs. The fourth interval includes the cold ischemic interval that covers the period after hypothermic washout, ends with the transplantation procedure, and is the area to which most attention has been directed in the past with regard to organ preservation. Finally, the fifth interval is the transplantation procedure itself in which rough handling, a lengthy anastomotic time, release of bradykinins, and other factors are all possible causes

of organ injury. Improvements in limiting the organ damage incurred during the agonal period, the warm ischemic interval, and at the time of kidney removal are probably of much more clinical significance than the method of organ preservation during the cold ischemic interval. Many of the improvements attributed to continuous pulsatile perfusion methods may be due to the more optimal circumstances of organ harvesting.

A factor that needs emphasis concerns the application of experimental findings in the dog and other animals to the human clinical situation. Studies of organ preservation in the dog are not necessarily applicable to man; indeed the dog may be a more difficult animal model than man in which to perform whole organ preservation. Basic physiologic principles of cellular and tissue damage and decreasing function are not completely appreciated, and the effects of attempts at organ storage such as hypothermia and hyperbaria, initial and continuous organ perfusion, the use of metabolic inhibitors, and the value of perfusate solutions are not well defined. Consequently, attempts at improving organ preservation often follow an empiric course with many more failures than successes and a seemingly unending array of various storage methods.

The basic research model for testing various storage systems has been autotransplantation following the period of storage. In the evaluation of kidney transplants either an immediate or delayed contralateral nephrectomy is performed. This permits assessment of the minimal requirements for preserving an organ that must function immediately or that will recover after a period of functional insufficiency. A much more sophisticated but time-consuming model is the use of the split-bladder preparation that allows comparison of a stored autograft with the function of a normal kidney in the same electrolytic and volumetric environment.[69]

The techniques of organ preservation used in renal transplantation involve the surface cooling technique without an initial washout of the kidney, a hypothermic washout of the kidney followed by surface cooling and storage, and continuous hypothermic pulsatile perfusion. A variety of washout and perfusate solutions have been employed, along with various pharmacologic agents that are used to inhibit metabolism, to stabilize membranes, to permit vasodilatation, and to prevent blood coagulation. Storage under hyperbaric conditions either with or without oxygen has been employed in the clinical setting and appears to be of benefit in some situations, especially with liver preservation.[14, 15, 43]

The present status of human organ preservation must be evaluated by examination of the results obtained in clinical situations. It is recognized that the variables in the clinical setting are not as well controlled as in the experimental animal model, and therefore the differences in methods of organ preservation are more difficult to evaluate under clinical conditions. Clinical application of basic principles learned from experiments performed in the animal, particularly the dog, have been and will continue to be important. However, the present state of the art and its application to clinical transplantation must be viewed with regard to what is practically feasible at the present time under clinical conditions. The functional results of organ preservation can be classified into several categories. Some kidneys will have excellent immediate function with no need for any dialysis. Others will have a period of temporary dysfunction but also do not require dialysis. Some kidneys will require temporary dialysis until the kidney regains

sufficient function to support the patient. The worst result is, of course, the kidney that never regains sufficient function to support life. The effects of vascular complications, ureteral complications, and hyperacute, accelerated, or acute rejection reactions are often difficult to separate from the damaging effects on the kidney from organ preservation. We have difficulty in accurately diagnosing acute rejection reactions in kidneys with acute tubular necrosis after renal transplantation.

In an attempt to place the present status of human organ preservation in proper perspective, we shall attempt to focus on the results of clinical methods of organ preservation rather than reviewing the voluminous material available on numerous experimental models.

Surface cooling

Surface cooling alone without initial washout has been used successfully in human renal cadaver transplants, but the results are generally inferior to other methods of preservation.[28] This method is no longer used with any frequency because of the better results obtained when organs are perfused prior to cold storage.

Of interest is the theoretic need to warm the kidney prior to reconstituting blood flow from the recipient into the transplanted organ. The possible existence of MN incompatibility and the activation of cold antibodies by the hypothermic transplanted kidney has been discussed by Dempster.[23] He has advocated a rapid rewarming process involving a small volume of washout solution that would not prolong operating time, but that would block the effects of any possible cold antibody reaction and also ensure that the renal peripheral resistance is reduced as much as possible. This aspect of renal transplantation has received little attention in the recent literature.

Hypothermic washout and surface cooling

The differences between intra- and extracellular solutions used for initial flushing of kidneys have been previously mentioned. An increasing experience with an intracellular perfusate (Collins' solution) attests to the satisfactory clinical results with this method. Most data support the conclusion that kidney preservation with Collins' solution is distinctly superior to that with Ringer's lactate with or without additions such as albumin, bicarbonate, heparin, or procaine.[55, 70] Human kidneys stored with Collins' solution have resulted in a 46% immediate function rate after 9 to 16 hr of cold ischemia when the warm ischemia has been less than 10 min. The ultimate function of all grafts regardless of warm ischemia time and with 16 hr or less of cold ischemia has been 90%.[31] Ultimate function rates of 85% to 100% with 30 min or less of warm ischemia and 15 hr or less of total ischemia can be expected with the use of Collins' solution.[28, 55, 70] Methods of perfusion and surface cooling with storage in insulated containers have been discussed previously.

Pulsatile perfusion

Pulsatile perfusion with cryoprecipitated plasma is the only proved method for long-term human kidney preservation. Human kidneys stored for up to 72 hr by this method have functioned successfully after transplantation. Belzer and

various associates[8, 11, 12] have contributed significantly to the development of renal storage by hypothermic pulsatile perfusion and have reported an experience with 210 human cadaver kidneys. They have identified fat emboli to be a principal cause of rising perfusion pressure and edema in isolated organs perfused with plasma or whole blood. Elimination of lipoproteins by filtering cryoprecipitated plasma has alleviated this problem.[7] The identification of vasoconstriction in the agonal phase prior to donor organ harvesting and its treatment with phenoxybenzamine have been additional important contributions.[11] When phenoxybenzamine is used prior to death, dialysis following the transplantation of organs stored on the Belzer perfusion machine for an average of 27 hr with 29 min of warm ischemia is required in 17% of cases.[12]

The MOX-100* continuous pulsatile preservation apparatus developed at the University of Minnesota employs cryoprecipitated plasma and has been associated with an 84% to 90% usable kidney rate.[47] Eventually 91% to 97% of transplanted kidneys function, and 60% to 82% do so immediately. These better function rates are associated with no warm ischemia and pulsatile perfusion started immediately after nephrectomy.

Sterling et al.[67] have compared the MOX-100 and the LI-400 Belzer machine† and could find no significant differences between these two machines, which are the most commonly used continuous pulsatile perfusion machines in clinical transplantation. The rate of immediate function following preservation was 65% on the MOX-100 and 61% on the LI-400.

Aside from the preservation of organs, pulsatile perfusion has permitted the assessment of organ viability. This is a definite advantage in situations where organ harvesting has not been optimal and the viability of the kidneys is in question. Because of the demand for cadaver kidneys, it is necessary to harvest all potentially usable organs, which in many cases may involve kidneys that are of borderline quality. If kidneys could be harvested under the best conditions and the total ischemia time kept to less than 5 hr, hypothermic pulsatile perfusion would probably be unnecessary.[67]

Clark and associates[18] have recently challenged the concept that pulsatile perfusion permits testing of organ viability and thus the elimination of nonviable organs. They demonstrated that with the use of an intracellular washout solution and surface cooling, the kidney transplant survival rates were the same or better than with perfusion on the Belzer machine. However, the comparison was between a shorter period of cold ischemia (mean 5.8 hr) for the Collins' preserved kidneys and a longer period (mean 21.5 hr) for the Belzer perfused kidneys. Good results for human cadaver kidneys stored in Collins' solution have been reported for ischemia times of up to 16 hr.[28, 31] Information concerning longer periods of storage with Collins' solution is not available, but experimental data exist that indicate good function may be expected with up to 30 hr of ischemia, provided the warm ischemia time is kept short.[19] The tenth report of the *Human Renal Transplant Registry* shows that the 1-year survival rates of kidneys stored by pulsatile perfusion and those stored by surface cooling are the same.[4]

*Waters Instruments, Inc., Rochester, Minn.
†Life Medical Systems, Inc., Evanston, Ill.

A combination of hypothermia storage plus pulsatile perfusion has been demonstrated to be successful.[34] Sterling et al.[66] studied 34 cadaver kidneys in which preservation times up to 50.5 hr occurred. Pulsatile perfusion always followed the hypothermic storage, in which Ringer's lactate with albumin, heparin, and procaine or dextran buffered with bicarbonate was used. Acute tubular necrosis occurred when the warm ischemia time exceeded 15 min, the total ischemia time was greater than 7 hr, the diastolic pressures were more than 20 mm Hg during pulsatile preservation, or flow rates were less than 80 ml/min. Magnusson and Kiser[42] have not found any direct correlation between the cold ischemia time prior to pulsatile perfusion and the subsequent perfusion characteristics or function of the kidney after transplantation. Kauffman et al.[33] also confirmed the feasibility of using combined techniques of iced saline slush storage and pulsatile perfusion and attributed some of their success to an electrolyte flush of the kidney after pulsatile perfusion and before storage in slush. These results in humans are contrary to the data in canine models where combined techniques of pulsatile perfusion followed by slush storage are unsatisfactory.[59, 78] Although a single human kidney will tolerate a combination of preservation techniques, this may not be the optimum method of storage.[10] Nevertheless, this method does facilitate the storing of kidneys and helps to assure that none are wasted.

Technique of pulsatile perfusion

Several types of pulsatile perfusion equipment have been used to preserve human and cadaver kidneys.[12, 47, 48] All these have advantages and disadvantages, and all have in common a basic perfusion circuit that includes a venous reservoir, a membrane oxygenator, a pulsatile perfusion pump, a heat exchanger, and a chamber to store the kidneys. The Belzer pulsatile perfusion apparatus has been used more frequently than the others in human renal transplantations and is the type with which we have had experience (Fig. 5-4).

The advantages of continuous pulsatile perfusion over surface cooling storage include (1) long storage periods (maximum of 72 hr), (2) organ viability testing, (3) repair of organ damage (vasospasm), and (4) potential for alteration of organ antigenicity (passive enhancement). Only the first three are qualified successes. The reversal of renal vasospasm is possible, but true repair of tissue injury is probably unlikely.[64] The only storage method permitting repair of damaged kidneys is the in vivo storage in an intermediate host.[1] The ability to alter the antigenicity of human kidneys is not a clinical reality at present.

Potential disadvantages of continuous hypothermic pulsatile perfusion are (1) the additional cost (equipment, expendables, and technicians), (2) infection, and (3) damage to the kidney (air embolus, etc.). Only the additional cost has proved to be a significant disadvantage. Perfusate cultures have been consistently negative if proper sterile techniques are practiced. Air embolus and other forms of injury to the kidney over and above that incurred by surface cooling alone are insignificant. Although immobility of the equipment was once a disadvantage, now portable perfusion equipment is available that can be hand carried and stored on or under an airplane seat.

Perfusate. Although whole or diluted blood,[3, 30] electrolyte solutions,[17] and tissue culture media[29] have been used for pulsatile perfusion of organs, it re-

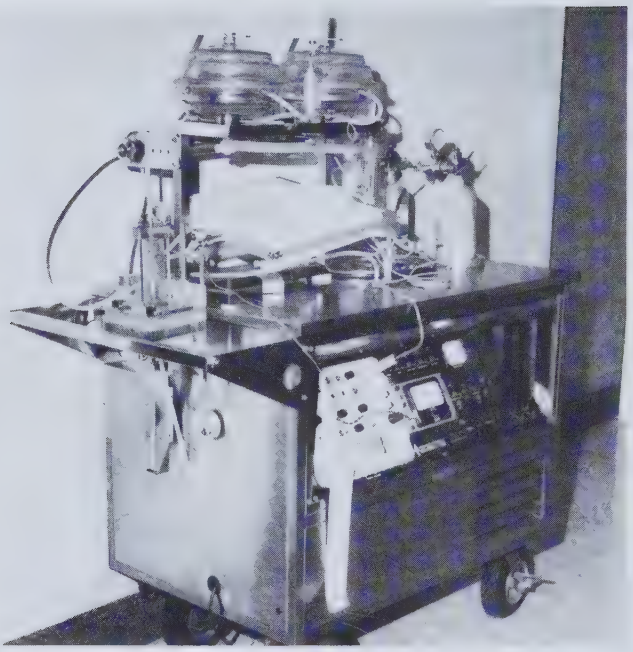


Fig. 5-4. Belzer pulsatile perfusion machine LI-400.

mained for Belzer and various associates[6, 7, 12] to advocate cryoprecipitated type-specific or AB-positive plasma as the perfusate of choice. Fat emboli are one of the principal reasons for the rising perfusion pressure and the interstitial edema associated with plasma perfusates. Denaturation of lipoproteins by freezing to –20° C and rapid thawing permits the aggregation of the low density, less stable lipoprotein group. Microfiltration then removes the precipitate and clears the plasma of approximately 30% to 35% of lipid components. The use of cryoprecipitated plasma in conjunction with the employment of the membrane oxygenator has effectively eliminated fat embolization of cadaver kidneys stored by pulsatile perfusion.[7]

Plasma protein fraction (PPF) has been demonstrated to be an effective perfusate in the canine model, and has only recently been used in human renal perfusion.[32] It is prepared by extracting heat-labile fibrinogen and gamma globulin, followed by incubation at 60° C for 10 hr to inactivate the serum hepatitis agent. PPF contains no fibrinogen, no gamma globulin, and no lipoproteins. It is free of serum hepatitis agent, is immediately available without requiring preliminary filtration, and can be used with simple and less expensive perfusion apparatus, because it does not become denatured or give rise to fat emboli. The effectiveness of this perfusate, however, remains to be proved under clinical circumstances.

The perfusate that we use for pulsatile perfusion of human cadaver kidney is prepared in a manner similar to the method described by Belzer and associates.[7, 8] One thousand milliliters of nonpooled frozen AB-positive or type-specific plasma is quickly thawed in a water bath at 60° to 70° C, carefully avoiding plasma temperatures over 38° C. The plasma is filtered through a microfilter to

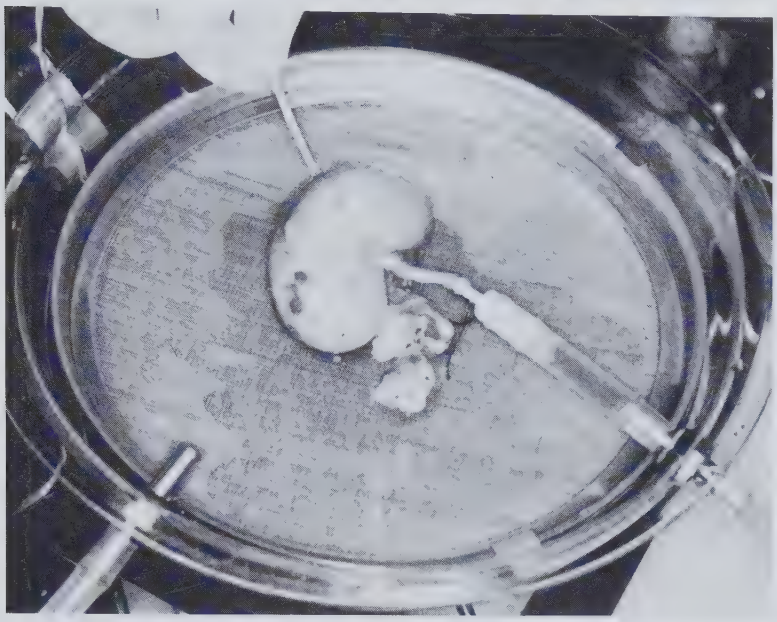


Fig. 5-5. Kidney being perfused on Belzer machine.

remove unstable lipoproteins and to sterilize the solution. The sodium and potassium concentrations are adjusted to 140 and 5 mEq/L, respectively, with distilled water. To each liter of perfusate is added 500,000 units of penicillin, 8 mg of dexamethasone, 2 ml of 50% magnesium sulfate, 120 units of regular insulin, and 12 mg of phenosulfonphthalein. Mannitol is not used.

Mechanics. The Belzer perfusion machine is primed with 800 ml of perfusate, the equipment checked for leaks, air bubbles removed from the circuit, and the temperature adjusted to 4° to 10° C. Cultures are obtained both before and after the perfusion procedure. Using sterile technique, a Teflon cannula is inserted into the renal artery and a silk suture placed around the most distal portion of the artery, securing the cannula. (The traumatized portion of the artery distal to the silk suture is resected before performing the arterial anastomosis to prevent possible stenosis of the suture line.) The kidney is placed in the organ receptacle, and the Teflon cannula is connected to the perfusion circuit (Fig. 5-5). Trapped air bubbles are removed from the cannula, and the artery is carefully inspected to avoid twisting. Double arteries are cannulated separately and joined by a Y connector or, alternately, a side-to-side anastomosis is performed, converting the vessels into a single lumen that can be cannulated. A temperature probe is placed under one kidney and the temperature is regulated. The pulse rate is kept at 60/min throughout the perfusion. Initially the systolic pressure is set at 60 mm Hg, and during the first hour the pressure is continuously reset at 60 mm Hg. After the first hour of perfusion, the pressure is no longer adjusted but is permitted to decrease spontaneously. There is no attempt to force flow rates. The membrane oxygenator using room air adequately oxygenates the perfusate, and there may be no need for additional oxygen. The pH, which is usually alkaline,

often tends to rise and is adjusted to 7.45 by adding carbon dioxide, thus increasing the P_{CO_2} in the membrane oxygenator.

Although some reports have indicated that changing the perfusate every 12 to 16 hr results in better preservation of dog kidneys,[2] others have not been able to confirm these findings.[77] We do not change the perfusate. If a kidney is to be stored by surface cooling during shipment to another transplantation center, the kidney is flushed with cold Collins' solution after removal from the perfusion apparatus.

Viability. Many methods have been proposed to determine during hypothermic pulsatile perfusion the potential for a viable functioning kidney after transplantation. While most of these methods monitor tissue damage, vascular resistance, and tissue edema, probably the tests with the best potential for predicting renal viability and performance after transplantation are those that measure renal function. Sell et al.[60] have demonstrated the presence of renal function in dog kidneys perfused at 24° C. Renal function of human kidneys perfused at 4° C is probably minimal and urine production merely an ultrafiltrate of the perfusate.[43] Tests involving kidney surface redox potential, tetrazolium bromide, biochemical studies of parenchymal kidney slices, and intracellular enzyme release into the perfusate have been used experimentally as indices of organ viability, but they are not frequently employed in assessing human cadaver kidneys.[60, 64]

The parameters most commonly monitored include pH changes, flow rates, perfusion pressure, lactic dehydrogenase (LDH) release, increases in renal weight, and general appearance of the kidney. A decrease in pH, especially during the first hour of perfusion, is associated with a poor outcome and is suggestive of tissue hypoxia and cellular damage, whereas good kidneys usually show a rise in pH of at least 0.1 unit during the first hour.[37] Flow rates greater than 100 ml/min are generally associated with good renal function. Kidneys with flows of 50 to 100 ml/min are satisfactory for transplantation, but postoperative acute tubular necrosis is likely. When flows are less than 50 ml/min, the kidneys are usually discarded.[8] Initial flow rates during the first or second hours of perfusion are probably most significant in estimating potential renal viability.[46] Diastolic perfusion pressures greater than 20 mm Hg and narrow pulse pressures are associated with a high incidence of acute tubular necrosis.[66] An LDH release of less than 20 units within the first hour of perfusion is typical of most usable kidneys and is moderately helpful in predicting renal viability.[37] An area of renal infarction will, however, cause abnormal elevations of LDH. A kidney that is flaccid, pale, and/or mottled is generally poorly perfused and portends a poor outcome. The turgid pulsatile kidney with good perfusion characteristics will often function promptly after transplantation. A kidney with a rising perfusion pressure should have its capsule incised to determine if a subcapsular effusion is the cause of the pressure increase.[76] A tense distended kidney with increased weight may be evidence of interstitial fluid accumulation indicative of poor viability. Evaluation of the potential functional recovery of perfused kidneys must consider the circumstances surrounding the organ harvesting. A kidney traumatically recovered after a long warm ischemic time in a donor with evidence of decreased renal function will often have poor posttransplant function even if the perfusion characteristics are good.

Approximately 15% to 30% of kidneys preserved by pulsatile perfusion are not used in renal transplantation, and half of these are discarded because of poor perfusion characteristics.[37, 42, 64] With better harvesting techniques, the relative proportion of usable kidneys is increasing. In our experience, only 10% of kidneys are not used, as most of the donors have been heart-beating cadavers. And, although our experience with community surgeons is limited, we have found that well-trained surgeons coached in the principles presented in this chapter have successfully harvested kidneys that functioned well after transplantation. It is hoped that dissemination of this information will increase the yield of viable cadaver organs.

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6

Surgical management of patients with reduced renal function

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There has been substantial progress in the past few decades in the care of patients with reduced renal function. Much of the progress is the consequence of more general use of better mechanical devices that can substitute for endogenous renal function either temporarily or permanently. Greater experience with permanent renal substitution therapy (chronic dialysis) has led to greater experience with the surgical care of patients with all degrees of reduced renal function. It is now possible to perform successfully any surgical procedure on patients with no kidneys at all; therefore reduced or absent renal function can no longer be considered a contraindication to any operation because although the risk may be large, the reward is great. The surgeon must carefully weigh the risk against the potential gain, but this can be applied to any operation.

During the past several years of experience with renal transplantation and the surgical care of patients requiring chronic hemodialysis, we have had the opportunity to perform or participate in the performance of a wide variety of operations on individuals without any endogenous renal function whatever. These include not only the renal transplantations, bilateral nephrectomies, splenectomies, arteriovenous access procedures, etc., required in the course of dialysis and transplantation, but also such diverse procedures as the evacuation of subdural hematoma, vagotomy and partial gastrectomy, colectomy, cholecystectomy, internal fixation of femoral neck fractures, parathyroidectomy, etc. This experience has led naturally into a much larger field, i.e., that of surgery in patients with all degrees of reduced renal function. This includes at one end of the spectrum the patient who has no clinical evidence of renal disease but has reduced creatinine clearance, and on the other end the patient whose survival

depends on repeated hemodialysis. This chaper will discuss the salient principles that must be followed in order to successfully treat this large group of individuals when they require surgery.

GENERAL CONSIDERATIONS

Etiologic classification of chronic renal disease

- I. Congenital
  - A. Agenesis or hypoplasia
  - B. Medullary cystic disease
  - C. Polycystic disease
- II. Primarily glomerular disease
  - A. Glomerulonephritis
    - 1. Acute, chronic, focal, rapidly progressive
    - 2. Basement membrane disease
    - 3. Goodpasture's disease
    - 4. Intercapillary glomerulosclerosis
- III. Primarily tubular disease
  - A. Chronic hypercalcemia
  - B. Chronic potassium depletion
  - C. Fanconi's syndrome and variants
  - D. Heavy metal poisons
- IV. Vascular disease
  - A. Renal artery stenosis
    - 1. Congenital
    - 2. Acquired
    - 3. Fibromuscular hyperplasia
  - B. Nephrosclerosis
  - C. Malignant hypertension
- V. Infections
  - A. Chronic pyelonephritis
  - B. Tuberculosis
- VI. Obstruction
  - A. Upper
    - 1. Calculi
    - 2. Retroperitoneal fibrosis
  - B. Lower
    - 1. Congenital anomalies
    - 2. Prostatism
    - 3. Urethral structure
- VII. Collagen disease
  - A. Scleroderma
  - B. Lupus erythematosus
  - C. Polyarteritis nodosa
- VIII. Metabolic disease
  - A. Amyloidosis
  - B. Phenacetin overdosage
  - C. Gout
  - D. Hyperparathyroidism
  - E. Sarcoidosis
  - F. Milk-alkali syndrome
- IX. Neoplasm
  - A. Benign
  - B. Malignant

The value to the surgeon of an etiologic diagnosis of renal disease is greatest when therapy is to be directed toward correcting the renal disease. For example,

transplantation in the patient with diabetic glomerulosclerosis carries an entirely different risk and prognosis than does transplantation in the patient with glomerulonephritis, and patients with pyelonephritis need bilateral nephrectomy prior to transplantation to prevent the unleashing of dormant infection by immunosuppressive therapy.

Careful study may be required to establish an etiologic diagnosis, but there are a number of clinical aphorisms that can be quite helpful:

1. The patient with anuria usually has an obstruction of the kidneys.
2. In far advanced renal disease the kidneys are usually small (on plain abdominal x-ray examination). An acute process should be suspected if they are normal in size. Exceptions include polycystic disease, lupus nephritis, and amyloidosis, all of which are relatively rare.
3. Small kidneys with massive proteinuria and reduced function have severe glomerular disease, usually some variety of glomerulonephritis or glomerulosclerosis.
4. Small kidneys with reduced function and minimal proteinuria have a larger component of tubular disease and are commonly produced by pyelonephritis or nephrosclerosis.
5. Modest reduction in renal function with the inability to concentrate urine represents tubular disease commonly produced by pyelonephritis, nephrocalcinosis, or drug toxicity.
6. Patients with reduced renal function and grade III or IV hypertensive retinopathy can be considered to have nephrosclerosis until proved otherwise.
7. Diabetics with renal disease can be considered to have glomerulosclerosis until proved otherwise.
8. Adult polycystic disease is produced by a dominant gene. The family history is usually positive, and the disease is frequently associated with hepatic cysts and aneurysms of the circle of Willis.
9. Familial nephritis is frequently associated with familial deafness.

It is more common for the general surgeon to be required to perform an operation on a patient with reduced renal function that is not directed toward improving renal function. In this instance a classification according to function is quite helpful.

Reduced renal function (reduced creatinine clearance)

A. Normal chemistries
B. Abnormal chemistries
   1. Azotemia
      a. Acute
      b. Chronic
   2. Uremia
      a. Acute
      b. Chronic

Note that reduced renal function is defined in the preceding outline as a decrease in creatinine clearance. Of course this is not strictly correct. There are many parameters of renal function other than creatinine clearance that are clinically useful. However, in so far as operative risk is concerned, the key is the clearance of waste products. This requires both the tubular flow of urine and

glomerular filtration. Renal tubular dysfunction is commonly observed in surgical patients. Problems related to tubular function can usually be dealt with rather simply by manipulation of either the patient's diet or parenteral fluid therapy; however, the inadequate clearance of wastes can only be managed by dialysis.

A functional classification provides considerable prognostic value. With an adequate assessment of renal function it is possible to predict fairly accurately what will happen to a patient with various changes in circumstances. From a pragmatic viewpoint, one kidney with a creatinine clearance of 30 ml/min will function much as any other kidney with a similar clearance. Any patient will become uremic (1) if the catabolic load exceeds his kidneys' functional capacity or (2) if his kidneys are adequately damaged either acutely or chronically. Frequently a combination of these events occurs in patients undergoing surgery. A patient in group A may not even become azotemic following an uncomplicated cholecystectomy but may rapidly become uremic should he develop a post-traumatic catabolic process such as might be produced by a subhepatic abscess.

PREOPERATIVE EVALUATION OF RENAL FUNCTION

The usual preoperative renal evaluation consists of a urinalysis and either a serum creatinine or blood urea nitrogen (BUN) determination. If normal, this is probably adequate for patients under 50 years of age who are to have operations that require a modest amount of trauma and patients who have no known diseases that reduce renal function. In numerous surgical emergencies,

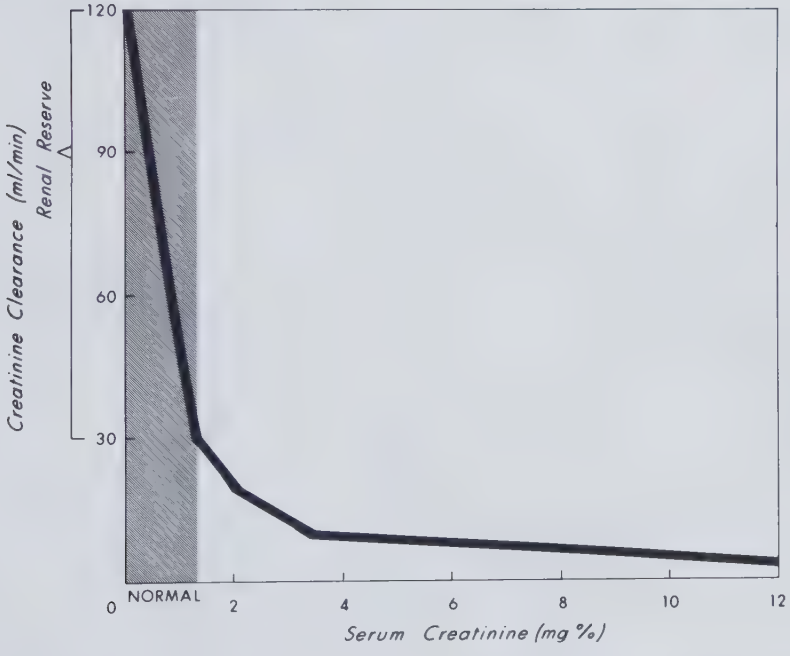

Fig. 6-1. Relationship between creatinine clearance (which reflects total renal function) and serum creatinine (which reflects the current state of renal compensation). (Based on data from Bernstein, L. M., et al.: Renal function and renal failure, Baltimore, 1965, The Williams & Wilkins Co.)

little if any renal evaluation is prudent since other lifesaving procedures take higher priority. However, in most other patients some additional information is indicated.

A person with normal kidneys possesses a great deal of renal functional capacity that is ordinarily not used. This extra function may be considered "renal reserve." The usual serum creatinine and BUN determinations do not become abnormal until all of this reserve has been exhausted.

Fig. 6-1 illustrates this fact. In our clinical laboratory the upper limit of normal for the serum creatinine level is 1.6 mg%. Note from Fig. 6-1 that a patient with a serum creatinine level below 1.6 mg% may have a creatinine clearance of 120 ml/min or one of 30 ml/min. In other words, 75% of the measured creatinine clearance can be considered renal reserve. Under normal metabolic conditions it is not required to preserve the internal environment. However, this reserve function is called on in times of rapid catabolism or following renal injury. Obviously, as the renal reserve is progressively diminished, smaller and smaller adverse changes in renal function or catabolic load result in renal failure. Therefore an estimate of the reserve a patient possesses can be quite illuminating and frequently leads the surgeon to take precautions aimed at preserving function that he might not ordinarily consider necessary. Measurement of the endogenous creatinine clearance is well suited for this evaluation. It is simple, inexpensive, readily available, and sufficiently accurate for general clinical use, and should probably be used more widely in preoperative evaluation.

An excellent way to evaluate renal function preoperatively is with a quantitative ^{131}I iodohippurate (Hippuran) scan utilizing a scintillation camera with a multichannel analyzer as advocated by Schlegel and various associates.[20, 32, 33] The

Table 6-1. Quantitative ^{131}I Hippuran scan of patient with nephrosclerosis and reduced renal function*

	Counts			
	Right		Left	
Time (min)	No.	%	No.	%
0-1	1164	42	1128	58
1-2	2318	47	2634	53
2-3	2734	49	2838	51
3-4	2247	52	2113	48
4-5	1810	58	1335	42
10	703	82	153	18
15	51	55	41	45

Bladder count in 28 min	7240
Bladder count after voiding	220
Residual urine calculated	25 ml
%Hippuran excreted in 30 min	
Voided	57%
Residual	1%
Total	58%

COMMENT: Decreased function bilaterally

*Data from Schlegel, J. U., New Orleans, La.

clearance of Hippuran differs from that of creatinine in that creatinine is virtually all cleared by glomerular filtration, whereas only 20% of the Hippuran is filtered and 80% is excreted by the tubules. Hippuran clearance more directly reflects renal blood flow than filtration; however, as long as the proportion of glomerular filtration:renal plasma flow (filtration fraction) is normal, Hippuran clearance will adequately reflect renal function. The quantitative scan reveals total renal function and the relative contribution of each kidney to total function. It may suggest renal artery stenosis, partial upper tract obstruction, or lower tract obstruction. The use of an analyzer oscilloscope provides a "picture" of the anatomic configuration of the renal mass. This procedure can be done in less than 1 hr and avoids the logistic problems of urine collection. An abbreviated protocol for treatment of a patient with nephrosclerosis is shown in Table 6-1.

The actual counts per minute are recorded for the right and left zones of interest in the second and fourth columns of the table. The percent of counts on each side are recorded for each counting interval, thus reflecting the relative contribution of each kidney to excretion of the labeled substance. There was relatively equal function on either side during the first 5 min, and the peak activity was between 2 and 3 min after injection. At the end of 28 min the patient voided and the urine sample was monitored. The counts in the sample, correlated to machine efficiency, allow the calculation of the amount of isotope excreted. The mean normal is 71% in our laboratory, the lower limit of normal being 66%. A postvoid scan of the bladder allows the calculation of milliliters of residual urine. This patient had a normal serum creatinine level and a creatinine clearance level of approximately 70 ml/min. The scan shows reduced function, but also shows it to be bilaterally reduced.

Table 6-2 presents data from a patient with an abdominal aortic aneurysm.

Table 6-2. Quantitative renal scan*

	Counts			
	Right		Left	
Time (min)	No.	%	No.	%
0-1	1194	61	770	39
1-2	2155	64	1229	36
2-3	2853	62	1724	38
3-4	3064	61	1982	39
4-5	3323	61	2208	39
10	3421	56	2718	47
15	2460	49	2501	51
25	1442	53	1279	47
35	605	45	748	55

Bladder count in 28 min	5135
Bladder count after voiding	1988
Residual urine calculated	218 ml
% Hippuran excreted in 30 min	
Voided	24%
Residual	15%
Total	39%

COMMENT: Partial obstruction of upper tract greater on left; significant bladder residual urine

*Data from Schlegel, J. U., New Orleans, La.

Three years previously he had a left ureteral stone. Operative removal led to a persistent ureterocutaneous fistula. This was ultimately treated by dividing the left ureter proximal to the fistula and performing a uretero-ureterostomy. Note that the maximal uptake of the labeled material does not occur until 10 min after injection, and the left kidney takes up the labeled material later and excretes it later than the right kidney. Although total excretion was low (39%), the creatinine clearances were over 100 ml min on two occasions; this discrepancy was due to partial ureteral obstruction.

Fig. 6-2 shows the intravenous pyelogram of the aforementioned patient, illustrating the partial obstruction. Since renal function was normal, he withstood his aneurysmectomy uneventfully. Intravenous furosemide was used intra-

Fig. 6-2. Intravenous pyelogram showing partial ureteral obstruction that accounts for delayed Hippuran excretion discussed in Table 6-2.

operatively as a precaution. The uretero-ureterostomy was not revised for fear of graft infection.

The quantitative scan has the disadvantage of requiring expensive and sophisticated instruments. It is more expensive than creatinine clearance measurement, but it also provides more information. If available, it can be quite helpful.

The following outline tabulates situations wherein some evaluation of renal reserve is in order. Group A represents patients who are likely to have decreased renal reserve; group B tabulates a group of operations that frequently lead to renal damage, and group C lists conditions in which the catabolic load may be greater than the kidneys can handle. These risks are additive; thus patients with more than one risk factor are more likely to develop renal failure.

Indications for thorough evaluation of renal function

A. High-risk patients
   1. Abnormal routine studies
      a. Urinalysis
      b. Serum creatinine
   2. Elderly ($>$ 50 years of age?)
   3. Diabetic
   4. Hypertensive
   5. Preoperative shock

B. High-risk operations
   1. Anesthesia $>$ 4-5 hr
   2. Blood loss $>$ 1500 ml
   3. Aortic
   4. Renal-vascular
   5. Pheochromocytoma

C. High-risk conditions
   1. Septic catabolism
   2. Posttraumatic pulmonary insufficiency

EFFECT OF VARIOUS FACTORS ASSOCIATED WITH SURGERY

It has been shown repeatedly that a surgical procedure usually results in a transient decrease in renal function. This is illustrated in Fig. 6-3. These data were obtained from a 72-year-old man who had an uneventful subtotal colectomy for multiple benign polyps. The systolic blood pressure was never below 100 mm and no blood was infused. Yet his creatinine clearance fell from 76 ml/min preoperatively to 37 ml/min on the first postoperative day. By the fifth day it had returned to baseline. This fall was almost a 50% reduction of creatinine clearance and is somewhat greater than usual. Dawson[13] found an average fall of 31% of the preoperative clearance in nonjaundiced patients having elective surgery. In jaundiced patients the decrease was 61%, which he suggested accounted for the increased risk of renal failure following such operations. Stahl and Stone[36] have confirmed these findings with respect to nonjaundiced patients. Although it is clear that this phenomenon occurs regularly, it is difficult to determine the relative participation of several factors to which the patient is exposed. Contraction of circulating blood volume by hemorrhage, dehydration, decreased cardiac output, or sequestration of fluid certainly is a major factor. Adequate hydration before and during the operation will minimize or prevent the decrease in creatinine clearance in many patients.[7, 19]

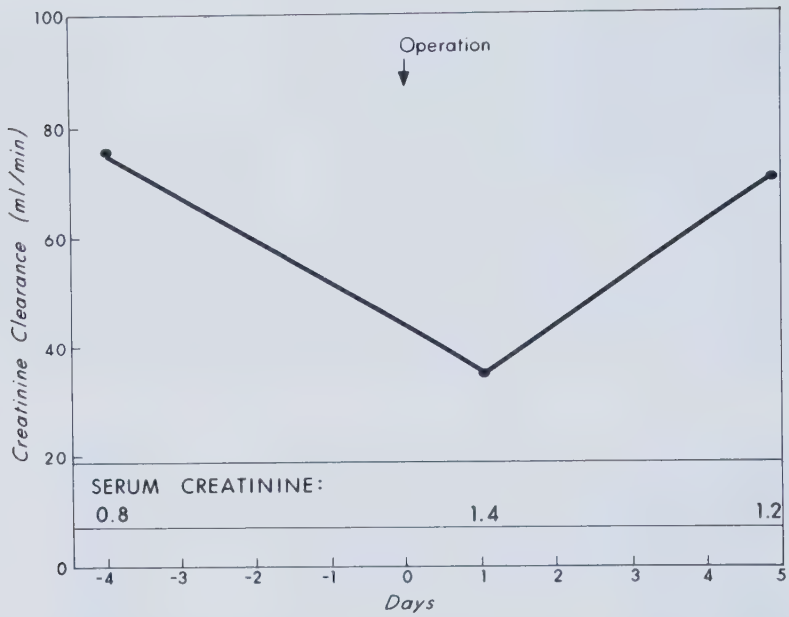

Fig. 6-3. Effect of surgery and events surrounding surgery in creatinine clearance when no special precautions are taken.

Anesthesia decreases creatinine clearance and urine output. This occurs in proportion to the depth of the anesthesia rather than the anesthetic agent and is probably related to a decrease in cardiac output.[7] The role of positive-pressure ventilation while under anesthesia is not clear, but in animals it alone produces oliguria.[16] Morphine, meperidine, and barbiturates also lead to oliguria and decreased creatinine clearance.[26] Morphine is particularly effective in this regard. The data in Fig. 6-3 were obtained from a patient who was anesthetized with nitrous oxide and multiple injections of morphine. Morphine may have been responsible for the greater than usual fall in creatinine clearance following the colectomy performed on this patient. Trauma alone initiates the same series of events.[8, 15, 29] Thus the patient undergoing surgery is subjected to many factors, all of which contrive to produce oliguria and decreased creatinine clearance. These changes in renal function ultimately reflect changes in renal blood flow.

It appears that these changes follow two patterns. If the changes in renal blood flow are "small," the physiologic response is mediated through the antidiuretic hormone, and restoration of effective circulating volume alone will reverse the process.[7, 16, 31] During this phase there is a preferential preservation of renal blood flow that seemingly could only result from decreased renal vascular resistance either absolutely or in proportion to greater vasoconstriction elsewhere. Although the renal blood flow is decreased, it is not decreased as much as the cardiac output.[31]

If the changes in renal blood flow are more severe, a number of additional physiologic responses occur. The renin-angiotensin-aldosterone systems and sympathetic and catecholamine responses are called into play. At this point

restoration of circulating blood volume will no longer reverse the process.[7, 16, 31] Renal blood flow may be improved little and at best only in proportion to improved cardiac output.[31] This is the result of sustained intrarenal vascular resistance and shunting of blood from the cortical-glomerular circulation to the inner cortical and medullary area, i.e., the Trueta shunts.[38] Presumably this is an extreme response that results in decreased glomerular filtration and the secretion of a highly concentrated urine. It is doubtful that this process alone will result in renal damage without some additional factor such as persistent inadequate circulating blood volume, multiple transfusions, sepsis, antibiotic therapy, disseminated intravascular coagulation, or trauma. The exact circumstances in which these factors are active are not well delineated, and undoubtedly all of the possible factors are not known. Furthermore, it is frequently impossible to avoid them. Therefore it seems appropriate to reverse or avoid altogether this dangerous train of events, particularly when an operation on a patient with reduced renal function is involved.

Blood transfusions bear special comment. The relationship of hemolytic transfusion reactions to acute renal damage is thoroughly established. However, it should not be assumed that a transfusion reaction is necessary for renal damage to occur. Although not proved by direct evidence, it is likely that much of the renal damage observed following multiple transfusion is a result of the trapping within the renal vasculature of damaged or dead cellular elements of blood, thus producing further ischemic damage. In this context renal damage may be likened to the pulmonary insufficiency that follows massive transfusion.

PHARMACOLOGIC AGENTS IN COMMON USE

Diuretics. Mannitol and furosemide are the two agents most commonly used to preserve renal function. Mannitol is an osmotic diuretic. Its distribution is limited to the extracellular space. When given intravenously it increases renal blood flow and creatinine clearance. There is some contradictory evidence on this point,[34] but most investigators have reached this conclusion. There seems to be no doubt concerning this point under conditions of low renal blood flow. Most of the effect of mannitol may be due to increased cardiac output secondary to the movement of fluid from intracellular to extracellular space.[6, 22, 28, 29, 31] Once in the renal tubules, mannitol is not reabsorbed, and it produces a large volume of renal tubular urine flow. It is relatively nontoxic and can be given in large quantities. As much as 100 Gm/day can be given safely.[4]

Mannitol has been used more extensively than furosemide, and there is more clinical experience with it, especially in large doses. Its major disadvantage lies in the problem produced when oliguria does not respond to mannitol infusion. The mannitol will remain in the circulation, expand the blood volume, and perhaps overload the cardiovascular system. An anatomic abnormality called mannitol nephrosis is produced by mannitol infusions. It is characterized by large vacuoles within renal cells, but this apparently does not affect function detrimentally.[37]

Furosemide is a newer drug. It produces diuresis by preventing the tubular reabsorption of sodium. It has the additional property of increasing renal blood flow and glomerular filtration in chronic as well as acute renal failure.[12, 18, 21, 25, 30, 35] The mechanism of this process is unclear, but it appears to involve a de-

Table 6-3.* Antibiotic usage in patients with renal insufficiency

Group	Antibiotic	Serum half-life (hr)		Recommended dosage for adults (70 kg)			Serious adverse effects†
		Normal subject	Anuric patient	Normal renal function	Serum creatinine, 2-10 mg%	Serum creatinine, 10 mg%	
Major reduction in dosage	Amphotericin B	Prolonged	?	Up to 1 mg/kg/day (IV)	Up to 0.5 mg/kg every 2-3 days‡	Up to 0.5 mg/kg every 3-7 days‡	Nephrotoxicity
	Colistimethate	2-3	48-72	1.00-1.25 mg/kg every 6 hr (IM)	1.00-1.25 mg/kg every 24 hr‡§	1.00-1.25 mg/kg every 48-72 hr	Nephrotoxicity; paresthesia
	Demethylchlortetracycline	12	?	0.3 Gm every 6 hr (PO)	0.3 Gm every 24-48 hr‡§	0.3 Gm every 72-96 hr‡§	Hepatotoxicity
	Gentamicin	2	48-72	80 mg every 8 hr (IM)	80 mg every 12-24 hr	80 mg every 48 hr	Nephrotoxicity; ototoxicity (vestibular)
	Kanamycin	3	72-96	7 mg/kg every 12 hr (IM)	7 mg/kg every 36-72 hr‡§	7 mg/kg every 96 hr‡§	Nephrotoxicity; ototoxicity (cochlear)
	Oxytetracycline	10	?	0.5 Gm every 6 hr (PO); 8 mg/kg every 6 hr (IV)	0.5 Gm every 24-48 hr‡	0.5 Gm every 72-96 hr‡	Hepatotoxicity
	Polymyxin B	6	48-72	0.8 mg/kg every 8 hr (IM)	0.8 mg/kg every 24-72 hr‡§	0.8 mg/kg every 24-96 hr‡§	Nephrotoxicity; paresthesia
	Streptomycin	2-3	52-100	0.5 Gm every 6 hr (IM)	0.5 Gm every 36-48 hr‡§	0.5 Gm every 72 hr‡§	Ototoxicity (vestibular)
	Tetracycline	8.5	57-108	0.5 Gm every 6 hr (PO); 8 mg/kg every 6 hr (IV)	0.5 Gm every 24-48 hr‡	0.5 Gm every 72-96 hr	Hepatotoxicity
	Vancomycin	6	?	7 mg/kg every 6 hr (IV)	7 mg/kg every 24-48 hr‡§	7 mg/kg every 72-96 hr‡§	Ototoxicity (cochlear)
Moderate reduction in dosage	Carbenicillin	0.5-1.0	12.5	1.0 Gm/hr (IV)	1.0 Gm every 2-4 hr‡	2.0 Gm every 8 hr	Urticaria; asymptomatic; ↑SGOT
	Cephaloridine	1.5	20-23	12.5 mg/kg every 6 hr (IM)	12.5 mg/kg every 12 hr‡	12.5 mg/kg every 24 hr	Hypersensitivity; nephrotoxicity
	Cephalothin	0.5	3-18	15-35 mg/kg every 4 hr (IV)	20 mg/kg every 6-8 hr‡	20 mg/kg every 24 hr	Hypersensitivity
	Penicillin G	0.5	7-10	Up to 2,000,000 units every 2 hr (IV)	Up to 2,000,000 units every 4-12 hr‡	Up to 2,000,000 units every 12 hr	Hypersensitivity; seizures

None or minor reduction in dosage	Ampicillin	0.5-1.0‖	?	15-30 mg/kg every 4-6 hr (PO or IV)	At 30 mg/kg reduce to every 6 hr§	At 30 mg/kg reduce to every 8 hr‡	Hypersensitivity; seizures
	Chloramphenicol			3.5-10.0 mg/kg every 6 hr (PO or IV)	Not required	Not required	Hematotoxicity
	Active	2-3	3-4				
	Conjugate	4-5	70-150				
	Cloxacillin	0.5-2.0‖	?	7-20 mg/kg every 4-6 hr (PO or IV)	Not required	Not required	Hypersensitivity
	Erythromycin	1.4	5-6	7 mg/kg every 6 hr (PO or IV)	Not required	Not required	Phlebitis
	Isoniazid	1-4	?	3-5 mg/kg/day (PO); usually 300 mg/day	Probably should not exceed 300 mg/day‡	Probably should not exceed 300 mg/day‡	Peripheral neuropathy
	Lincomycin	4.5	10-13	7 mg/kg every 6 hr (PO, IM, or IV)	Not required	7 mg/kg every 8-12 hr	Gastrointestinal
	Methicillin	0.5	4	20-40 mg/kg every 4-6 hr (IV)	Not required	Probably should not exceed 12 Gm/day‡	Hypersensitivity; nephrotoxicity
	Nafcillin	0.5-1.0‖	?	7-20 mg/kg every 4-6 hr (PO or IV)	Not required	Not required	Hypersensitivity
	Novobiocin	2	?	7 mg/kg every 6 hr (PO or IV)	Not required	Not required	Skin rash; jaundice
	Oxacillin	0.5	2	7-20 mg/kg every 4-6 hr (PO or IV)	Not required	Not required	Hypersensitivity
Agents that should not be used	Bacitracin	1.5	?	25,000 units every 6 hr (IM)	Use alternative agent	Use alternative agent	Nephrotoxicity
	Chlortetracycline	5.6	6.8-11.0	0.5 Gm every 6 hr (PO)	Use alternative agent¶	Use alternative agent¶	—

*From Seldin, D. W., Carter, N. W., and Rector, F. C., Jr.: In Strauss, M. B., and Welt, L. G., editors: Diseases of the kidney, vol. 1, Boston, 1971, Little, Brown & Co.; data from various sources.

†Adverse effects may be either frequent or infrequent.

‡Recommendations represent estimates that seem reasonable; actual confirmatory studies have not been done.

§An initial "loading dose" of twice the dosage listed is recommended in serious infections.

‖Estimated from published disappearance curves.

¶Metabolic effects may occur despite rapid inactivation.

crease in intrarenal vascular resistance, and it is accompanied by increased cortical blood flow.[22] Furosemide can be given in very large doses; as much as 3200 mg/day has been administered by Cantarovich et al.[12] Toxic effects appear to be restricted to transient and reversible hearing defects.[39]

These agents can be used to prevent the sequence of surgical events from proceeding to the stage of renin-angiotensin-aldosterone release, etc. and thereby to avoid the train of events that provides the setting for acute renal failure. They may also be useful in interrupting this chain of events once it has been set in motion, as will be discussed subsequently.

Antibiotics. Antibiotic therapy must be modified in patients with reduced renal function. Many antibiotics are partly or completely excreted by the kidneys and toxicity may result from the use of usual doses. Table 6-3 is a compilation of data relating dosage to serum creatinine levels.

SURGICAL MANAGEMENT OF PATIENTS WITH REDUCED RENAL FUNCTION BUT NORMAL CHEMISTRIES

Patients with creatinine clearances between 70 (lower limit of normal) and 25 ml/min can be expected to tolerate almost any surgical procedure without artificial dialysis, provided additional renal damage is prevented and no excessive catabolic load develops.

Adequate preoperative hydration appears a critical and yet simple matter that is too often overlooked. It is most important that patients with reduced renal function arrive in the operating room adequately hydrated and producing urine at a good rate. About 1 ml/min seems a minimal figure. This can usually be obtained by administering 2000 ml of fluid during the night before surgery. Furthermore, patients should be encouraged to drink fluids liberally until bedtime the evening before surgery. For patients with creatinine clearances between 40 and 70 ml/min having routine elective procedures, this is usually all that is required. These patients need not undergo catheterization, but urine volume should be carefully observed in the postoperative period, and the serum creatinine should be determined often enough to recognize any undesirable trend.

We have arbitrarily considered a creatinine clearance of 40 ml/min or less as an indication for using mannitol or furosemide therapy intraoperatively as an additional means of preventing the transient deterioration of function so often produced. This rule of thumb came from the evidence that the postoperative creatinine clearance is frequently temporarily reduced to approximately two-thirds of the preoperative clearance.[13, 36] Hence a clearance of 40 ml/min or less might be reduced to one of less than 30 ml/min, which is the clearance at which azotemia usually develops. This form of treatment is also used in some patients whose clearances are greater than 40 ml/min, but who are undergoing emergency surgery when the renal function is unknown or who are having an operative procedure that is likely to be accompanied by renal damage.

An inlying urethral catheter is placed shortly after the induction of anesthesia; it is connected to a closed collecting system draining into a graduated reservoir. The reservoir is attached to the operating table in an appropriate position for observation by some member of the operating team, usually the anesthesiologist. A preparation of 10% mannitol in 0.45% NaCl in 5% dextrose

or 480 mg furosemide in 1000 ml normal saline solution is used intravenously. This is ordinarily attached "piggyback" to the usual intravenous line. One of these solutions is infused at a rate sufficient to maintain urine output at approximately 100 ml/hr. The urine output is replaced with 0.5N or normal saline solution. Additional intravenous therapy is as indicated.

Fig. 6-4 shows data from a patient managed in the manner just explained. This patient is a 62-year-old male who had an abdominal aneurysmectomy. The average of three preoperative creatinine clearance measurements was 90 ml/min; hence he had normal function. He was chosen for presentation since the course of his case contrasts with that of the patient presented in Fig. 6-11. This patient was treated prophylactically, since he was having an operation that is frequently followed by acute renal failure. He received replacement fluids during his preoperative period of fasting and arrived at the operating table well hydrated, producing approximately 150 ml of urine/hr. During the 2 hr interval between his last micturition and uretheral catheterization at surgery he produced 300 ml of urine. This shows at the 0 hr in Fig. 6-4 as 150 ml/hr. He was given 40 mg of furosemide intravenously on induction of anesthesia, and an intravenous drip of furosemide was prepared. It was subsequently not used because of the sustained response to the initial treatment. The aorta was clamped during the second hour, which coincided with the maximal diuresis. The aorta was unclamped after 33 min of occlusion, and there followed a 15 min period without audible blood pressure. During the next 30 min some degree of hypotension persisted. Nevertheless, urine production continued at a rate of over 300 ml/hr.

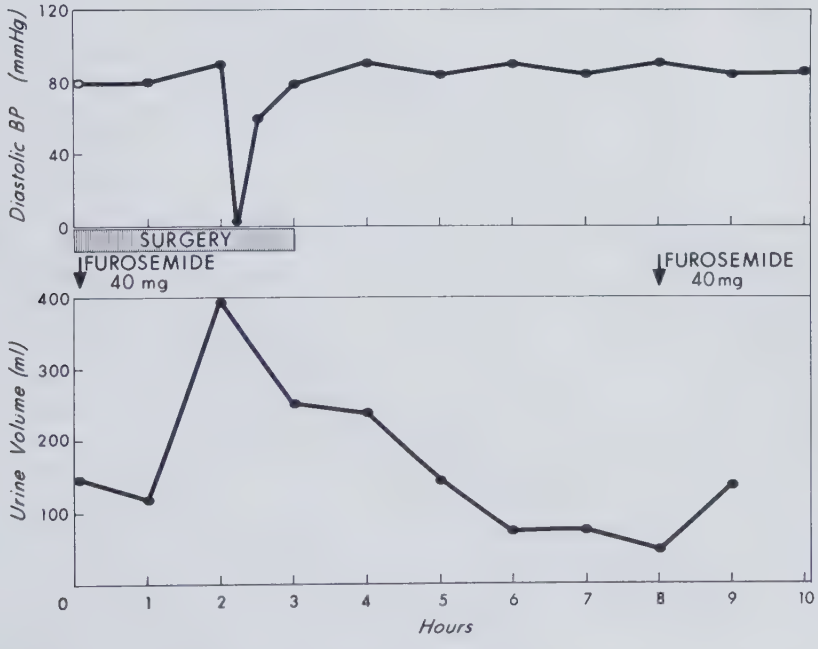

Fig. 6-4. Patient underwent abdominal aneurysmectomy and experienced 45 min of hypotension following removal of aortic clamp. Urine production continued and function was not affected. This is attributed to the presence of high renal blood flow with substantial diuresis at time hypotension occurred.

One subsequent injection of furosemide was given several hours later. The creatinine clearances determined on postoperative days 3, 4, 5, and 10 were 98, 96, 84, and 98 ml/min, respectively. Serum creatinine levels on these days were always below 1.0 mg%.

It is difficult to establish absolutely that this effort prevents renal decompensation because renal failure is unpredictable and the fact that a particular patient does not develop it is not evidence of the treatment's efficacy. Nevertheless, several authors have presented experiences supporting the value of such measures.[2-4, 6, 29] Their value is established in preventing acute renal failure in the case of hemolysis.[23, 27] In our opinion the bulk of the evidence supports the more general use of furosemide.

SURGERY IN AZOTEMIC PATIENTS

The term "azotemic" is used here to designate the condition in which serum creatinine and blood urea levels are elevated under normal metabolic conditions, but the patient does not present the clinical syndrome of uremia. Serum calcium levels may be decreased, and acidoses and anemia may exist, yet the patient remains asymptomatic. The severity of the azotemia will vary widely among individuals, and the creatinine clearance will vary between 5 and 30 ml/min.

These patients usually have an expanded blood volume and may have frank edema. If at all possible, some days of preoperative preparation may be very helpful. If emergency surgery is required, these patients should be handled as described in the previous section, but postoperative dialysis should be anticipated and preparations made to institute it early.

According to current evidence, a chronically diseased kidney may be viewed as one with an ever-decreasing number of relatively normally functioning nephrons. This contrasts with the older view that such a kidney consisted of a relatively large number of nephrons, all of which functioned to some extent but functioned abnormally. This work, pioneered by Bricker and various associates,[9-11] has demonstrated that an abnormal kidney in a normal environment produces qualitatively normal urine and has normal responses.

Thus a patient with 20% of his nephrons remaining produces urine qualitatively abnormal because the remaining nephrons are filtering greater volumes. The larger amount of filtrate presents such a large solute load to the tubular mechanisms that they are overwhelmed. In each remaining nephron there is a solute diuresis. Individuals thereby go through a period of time as renal disease progresses when they produce relatively large volumes of qualitatively poor urine. This has been called the "diuretic phase" or "dry phase" (referring to the patient) of chronic renal disease. Ultimately so few nephrons remain that, although they function heroically, oliguria develops. This patient then enters an "oliguric phase" of chronic failure and is usually edematous ("wet failure"). As a rule of thumb, the nonedematous patient is in a less advanced phase than the edematous patient (excluding the nephrotic syndrome). It is this group of patients with "dry" chronic failure that in past years was treated by expanding the fluid volume in order to induce greater diuresis. This was called "washing-out" the nitrogenous waste products. This therapeutic maneuver was rather risky since it was never possible to know how much more the renal mass could respond, and congestive heart failure was always a hazard. Furosemide has

provided a means of producing the "washing-out" that is less risky and is also useful in the more advanced wet failure.

The preoperative preparation of such patients may require several days. After an evaluation of the clearing capacity, a search for factors that can be treated to improve function even slightly should be made. Urine cultures are in order even in the absence of pyuria. If the urine is infected, it should be sterilized and some time should be allowed to pass after sterilization so that improved function may develop. The improvement may be surprising. If 80% of an individual's nephrons are destroyed, an infection in the remaining 20% will affect renal function much more than a similar infection in more normal kidneys. An infusion pyelogram will provide valuable information concerning the relative function on each side, the size and contour of each kidney, the presence or absence of hydronephrosis, etc. A postvoid film will reasonably eliminate bladder neck obstruction and avoid the necessity for catheterization. Arteriograms may be indicated if there is disparity in renal size, function, or contour. Any correctable lesion that may improve renal function should be rectified if the operation required for nonrenal causes can reasonably be delayed.

Instrumentation and catheterization for diagnostic purposes should be avoided in patients with daily urine volumes of 1500 ml or less. Urinary infection in such individuals is quite dangerous and particularly difficult to eradicate.

After all corrective measures have been taken, if the patient is still azotemic a course of furosemide therapy is warranted. A starting dose of 160 mg/day is convenient. Muth[25] has shown that more effect is obtained if two thirds of the daily dose is given in the morning and one third 10 to 12 hr later. The dose may be doubled daily until the desired effect is obtained. A total of 2000 to 3000 mg/day can be given for several days if necessary. Intravenous therapy may be more effective and is also more convenient if more than 200 to 300 mg/day is given. It can be administered in a convenient vehicle such as normal saline solution or 5% glucose. A rate of 500 mg/hr seems safe, although some physicians have administered as much as 2000 mg in 30 min.[24]

In patients having creatinine clearances of 10 to 30 ml/min an increase in clearance should occur that is sufficient to lower the serum creatinine level somewhat. When maximal benefit has been obtained, the necessary operation should be performed. Intraoperative management should be as outlined earlier, and postoperative management should include continued diuresis until the major catabolic period has passed.

Careful observation and treatment of fluid and solute loss is critical throughout the treatment period. It is particularly important to remember that relatively large amounts of sodium will be excreted; this must be replaced to avoid serious complications. Improved creatinine clearances in patients treated with furosemide has been documented.[24, 35] Fig. 6-5 presents the data obtained by Morelli et al.[24] The data were obtained from 10 patients with nonedematous chronic renal disease. The mean-based creatinine clearance in this group was 7.4 ± 6.1 ml/min. Fig. 6-5 shows the mean changes in clearance for a 3 hr period following the intravenous administration of 2000 mg furosemide. These changes probably result from increased renal blood flow. The small number of nephrons functioning filter even more blood; thus the clearance is increased. As for the diuresis itself, the increased urine volume is of little importance in the "dry"

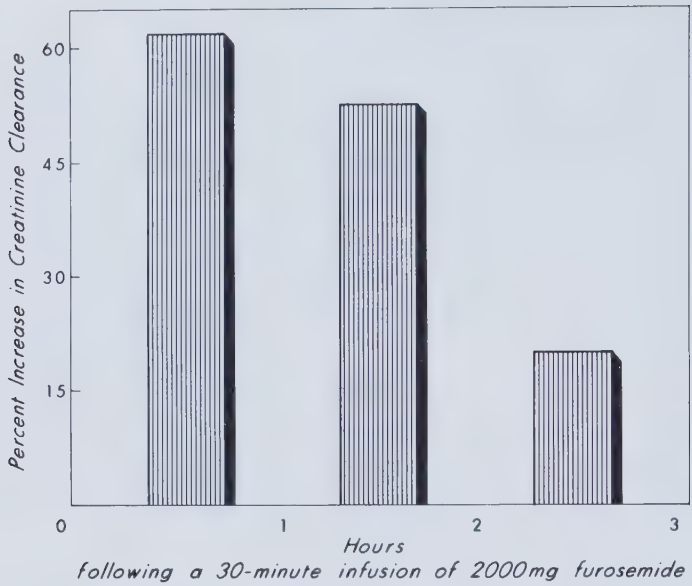

Fig. 6-5. Effect of furosemide on creatinine clearance in patients with advanced chronic renal disease. (Modified from Morelli, O. H., et al.: Postgrad. Med. J. 47[suppl.]:7, 1971.)

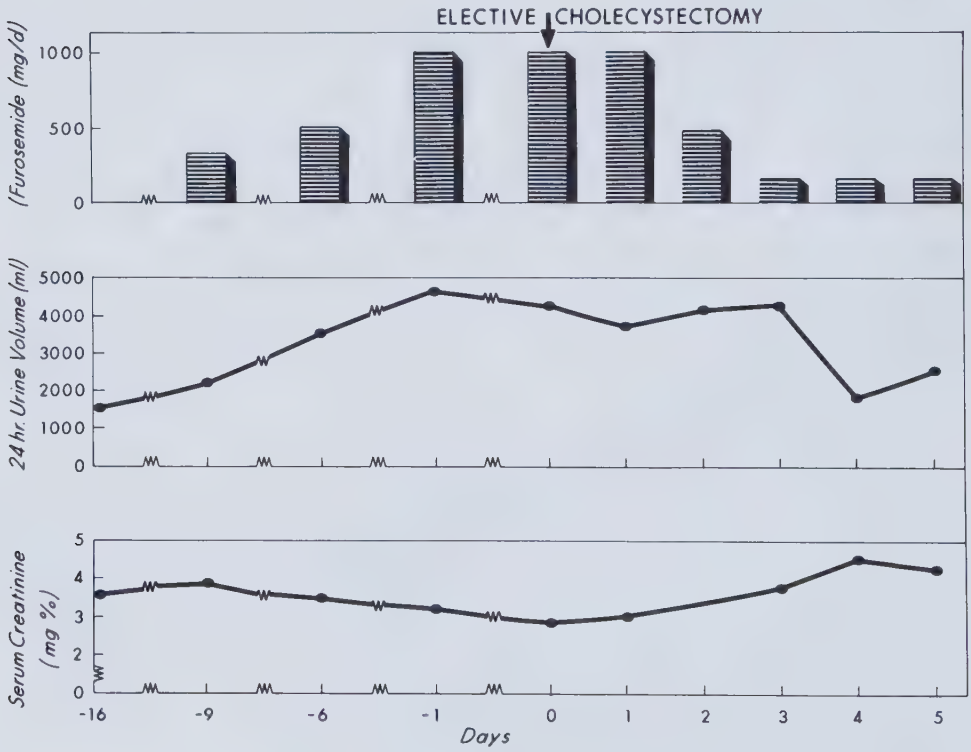

Fig. 6-6. Data from 70-year-old female who on admission had a creatinine clearance of 13 ml/min and who was treated preoperatively with large doses of furosemide.

azotemic patient; however, in edematous individuals it is an added dividend. As fluid is mobilized, the cardiodynamics improve, and renal blood flow may be improved on this basis.[25] Such an improvement is more sustained.

Fig. 6-6 depicts data from a 70-year-old female who was operated on electively for symptomatic cholelithiasis. She was known to have had a nephrectomy several years previously. A creatinine clearance test performed 16 days before surgery revealed a level of 13 ml/min. After urine cultures and renal scanning, the patient was started on a regimen of increasing furosemide therapy. She received 1000 mg/day 1 day preoperatively, on the day of the operation, and on the first postoperative day. Note the close correlation between increased dose, rising urine volume, and declining serum creatinine level. The creatinine clearance 1 day preoperatively was 18 ml/min. It was felt that maximal benefit had been gained, and elective cholecystectomy was performed. The patient recovered uneventfully. As furosemide therapy was decreased postoperatively, the serum creatinine level rose to a maximum of 4.6 mg% and then declined toward its preoperative value.

Dialysis facilities should be available for all azotemic patients who are operated on. With good management and preparation most patients with a basal clearance level above 10 ml/min will not require it, but if any major complication arises to increase the catabolic load or to injure the kidneys even modestly, dialysis will certainly be necessary temporarily. In individuals with a creatinine clearance of 10 ml/min or less, dialysis should be expected and performed in the early postoperative period.

If the preoperative creatinine level cannot be brought as low as 6 to 7 mg, if hyperkalemia is unmanageable, or if adequate diuresis cannot be obtained, two or three preoperative hemodialyses will bring the patient to surgery in much better condition.

Access to the circulation should be provided either before or during the necessary operation. A Scribner-type arteriovenous shunt is satisfactory. It is best placed in the forearm and must be protected intraoperatively. No intra-

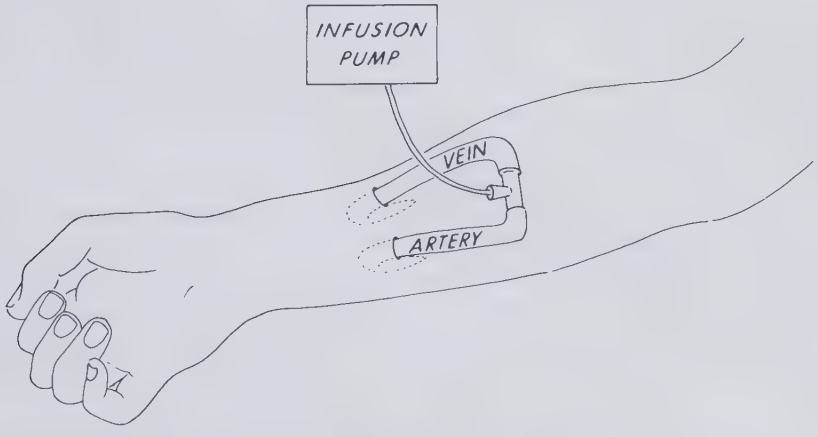

Fig. 6-7. Arteriovenous external shunt with T-tube for heparin infusion.

venous lines, blood pressure determinations, or other manipulation should be allowed in this extremity.

The trauma of surgery will cause a physiologic increase in coagulation, and the Scribner shunt frequently clots in the first 3 to 4 postoperative days. This may be prevented by interposing a T-tube arrangement between the limbs of the shunt to infuse dilute heparin as shown in Fig. 6-7. We prefer to use a shunt rather than to dialyze with Seldinger catheters inserted into the femoral vein for fear of thrombosis and subsequent embolism. We have used the femoral vein for dialysis in other settings, however, with satisfaction.

If no renal injury has been inflicted, dialysis will be necessary only until the catabolic load has returned to the preoperative situation.

SURGERY IN UREMIC PATIENTS

Patients who are uremic should by definition be on dialysis prior to operation. Surgery on such patients can be performed in its usual fashion with close attention to a relatively few major factors.

The adequacy of dialysis is a chief consideration. At surgery the patient should be in as near normal metabolic balance as is possible. This may require dialysis daily for several days preoperatively. On the other hand, if long-term management has been ideal, intensive preoperative dialysis may be unnecessary. Dialysis should always be performed the day before surgery, however.

The anemia of such patients may be profound, and the hematocrit will vary several percentage points, depending on fluid balance; i.e., immediately before dialysis the hematocrit may be 15% and immediately afterward 20% if an effort has been made to remove fluid. A preoperative hematocrit of 20% is quite high in our clinic, and one of 15% to 16% is usual.

It is a serious mistake to attempt to transfuse such patients to a more normal hematocrit. They are always overhydrated no matter how well they are dialyzed preoperatively. This is clearly observed in the early posttransplantation period. Fig. 6-8 demonstrates the phenomenon. The data are from a 20-year-old male who was dialyzed for some months before transplantation. His weight varied several pounds between the termination of one dialysis and the beginning of the next. However, he was at "dry" dialysis weight before the transplant.

The term "dry weight" to the nephrologist means that no additional fluid can be removed by ultrafiltration without producing hypotension. This by no means indicates true normal hydration. As noted in Fig. 6-8, an early diuresis occurred that resulted in a 7.5 pound weight loss by the tenth postoperative day. If all of this weight were fluid, it would equal 3500 ml. Part of the weight loss was due to the catabolic response to surgery and steroid administration, but a great proportion was due to the loss of excessive fluids that had been retained preoperatively primarily in the intracellular compartment. It requires longer for fluid to move out of the intracellular space into the extracellular space than from the latter across the dialyzing membrane. All of the intracellular fluid cannot be removed without producing hypotension. Perhaps this could be accomplished with virtually constant dialysis, but it is not accomplished by the current clinically practical methods of dialysis.

Therefore at surgery the uremic patient can be expected to have a profound anemia and an excess of body fluid. The blood volume will be normal or ex-

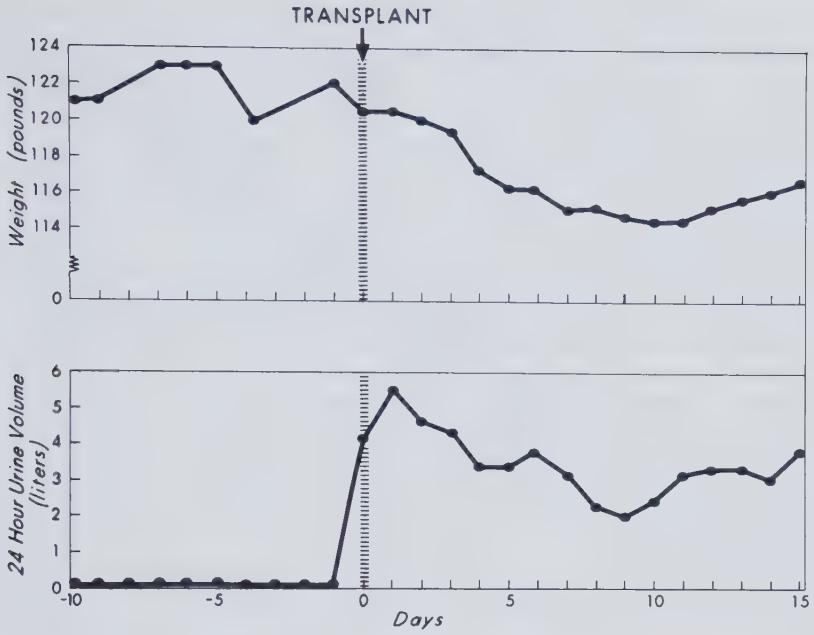

Fig. 6-8. Data showing typical weight loss from diuresis following renal transplant. Illustrates that patients on chronic dialysis are virtually always overhydrated. Before transplantation, patients undergo dialysis and their weights are recorded.

panded, depending on when it is measured in relation to dialysis. However, even when normal it is being expanded constantly by fluid from intracellular sources. It is hazardous to expand the blood volume even by packed erythrocytes because pulmonary edema is easily produced in this setting. It is our custom to replace blood loss at operation with packed erythrocytes, but it is frequently necessary to carefully instruct and observe the anesthesiologist to prevent excessive administration of a noncolloid solution.

Hemostasis is crucial. Uremic patients are known to bleed excessively. A study of the coagulation mechanism will usually not demonstrate any abnormality; nevertheless, clinically there is a defect. A compulsive effort must be made to obtain hemostasis. The wound must be "dry." We use the coagulating cautery for such patients and spend considerable time coagulating vessels that under other circumstances we would not hesitate to ignore. On occasion a continuous absorbable suture is used on muscle layers in order to obtain better hemostasis.

Postoperatively the frequency of dialysis will be dictated by the magnitude of the surgical procedure and the development of complications. Serum potassium can be partly controlled by sodium polystyrene sulfonate enemas and is not ordinarily a major problem. The dangers of hyperkalemia are so well understood that death from this source should never occur. The serum potassium level should be determined within a few hours of recovery from anesthesia and at least every 12 hr for two to three determinations. If the cation-exchange resin does not adequately control the serum potassium, dialysis is indicated.

Excessive fluid accumulation is not too common in such patients since

physicians are attuned to this problem. Fluids should be restricted to replacement of insensible loss plus loss from various tubes or drains minus about 300 ml of free water produced by catabolism. The contribution of free water may be considerably greater than 300 ml if the catabolic rate is excessive. Daily weight is the single most valuable determination in fluid management.

The rapidity of fluid production and weight gain and the accumulation of potassium and creatinine will dictate the frequency of dialysis. The principle to be applied is that the patient should be kept in as near normal physiologic balance as possible. A postoperative patient has sufficient burdens to bear in recovering from the surgical procedure without adding the problems of metabolic disturbances resulting from absent renal function. Dialysis should be performed frequently and for long periods.

Regional heparinization should be utilized for dialyses performed in the first 7 to 10 days following surgery. In the past, we have sometimes not used regional heparinization for dialyses performed over 72 hr after surgery. In most instances this is well tolerated but occasionally a serious wound hematoma will develop.

The postoperative course should not differ from that of any other surgical patient. Wound healing, infection, etc. seem uninfluenced by chronic renal disease.

ACUTE RENAL FAILURE IN THE SURGICAL PATIENT

The precise pathogenesis of acute renal failure remains in some doubt. The chief point of contention lies between the view that the basic defect is one of mechanical obstruction of damaged tubules and the view that the principal defect is a neurovascular process resulting in decreased glomerular filtration. In either case early efforts to increase renal blood flow, glomerular filtration, and tubular urine flow should be beneficial; this has proved true.

Acute renal failure can be considered as a process that develops over a finite period of time. Fig. 6-9 illustrates this concept. Renal function is represented on the ordinate and time on the abscissa. There is a period of time in the evolution of acute renal failure during which therapy can reverse the process (interval A). Later the process has produced sufficient damage to result in fixed failure (interval B). This concept was discussed nicely by Barry and Mallory[4] as early as 1962. They referred to interval A as functional failure and interval B as organic failure. The function phase is not purely a matter of prerenal failure since it is observable under other circumstances.

It is particularly important to recognize declining renal function as early as possible in order to begin therapy before organic failure is established. In some instances (in our opinion those that represent primarily prerenal failure), renal failure can be averted completely. In many others, however, the developing renal failure can be converted from oliguric renal failure to high-output renal failure. The latter has a much better prognosis and can usually be managed without dialysis.

An acceptable clinical protocol is as follows. When declining renal function is recognized, usually by declining renal volume, a test dose of 12.5 Gm of mannitol can be given intravenously. If the neck veins do not appear overly distended, 500 ml of normal saline solution can be infused over a period of

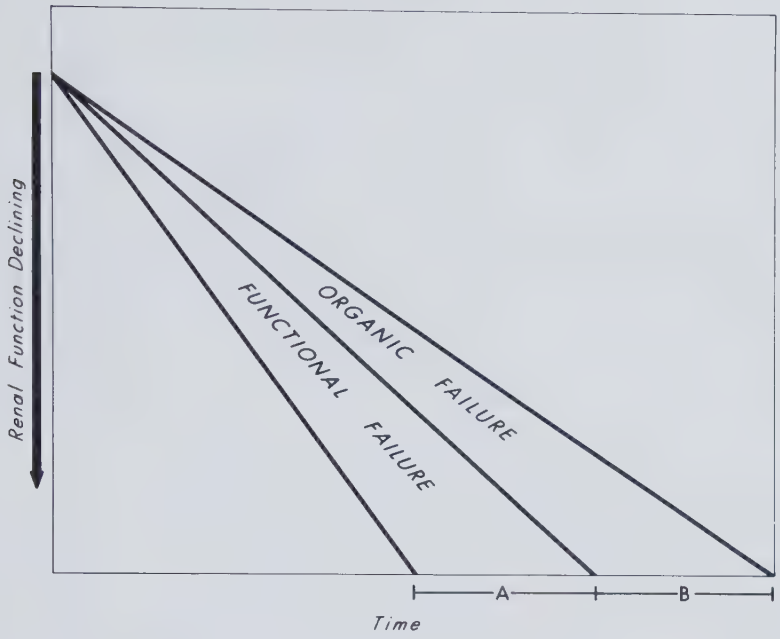

Fig. 6-9. Schematic concept of acute renal failure.

15 to 30 min immediately following the mannitol. If diuresis occurs, additional fluids may be administered as long as venous hypertension does not develop and the diuresis is maintained. These patients have prerenal failure. If the diuresis does not occur or if it is not maintained by hydration, furosemide or mannitol therapy is indicated. If mannitol is chosen, it can be given as a 10% solution at a rate titrated to produce an output of 50 to 100 ml/hr. No more than 100 Gm/day is recommended.[4] Fig. 6-10 shows the results in a patient treated with mannitol.

This patient, a 37-year-old male, received a renal allograft that was damaged by ischemia. Urine production began immediately but only 35 ml was produced during the first hour (Fig. 6-10, *A*). Two intravenous injections of 12.5 Gm of mannitol resulted in an increase in urine volume to 55 and 70 ml during the second and third hours, respectively. However, this was not sustained and for the next several hours urine volume averaged about 35 ml/hr despite adequate infusions of fluids. During the first postoperative day it was apparent the total renal function would be insufficient. An infusion of 10% mannitol in normal saline solution was begun. For 3 hr, 100 ml/hr was given. Subsequently, a volume was infused each hour to equal the previous hour's urine volume. A response began only after 5 hr had elapsed. On completion of the infusion, the output was sustained and no further mannitol was required.

The importance of this response can be seen in Fig. 6-10, *B* (the 24 hr period shown in Fig. 6-10, *A*, corresponds to day 1 in Fig. 6-10, *B*). On day 1 1200 ml of urine was produced, which included a period of 11 hr of mannitol infusion. The serum creatinine level on day 1 was 12 mg%, and the total creatinine excretion in the 1200 ml of urine was 800 mg. During day 2 creatinine excretion was 1000 mg in 2000 ml urine. These excretions correspond to endogenous

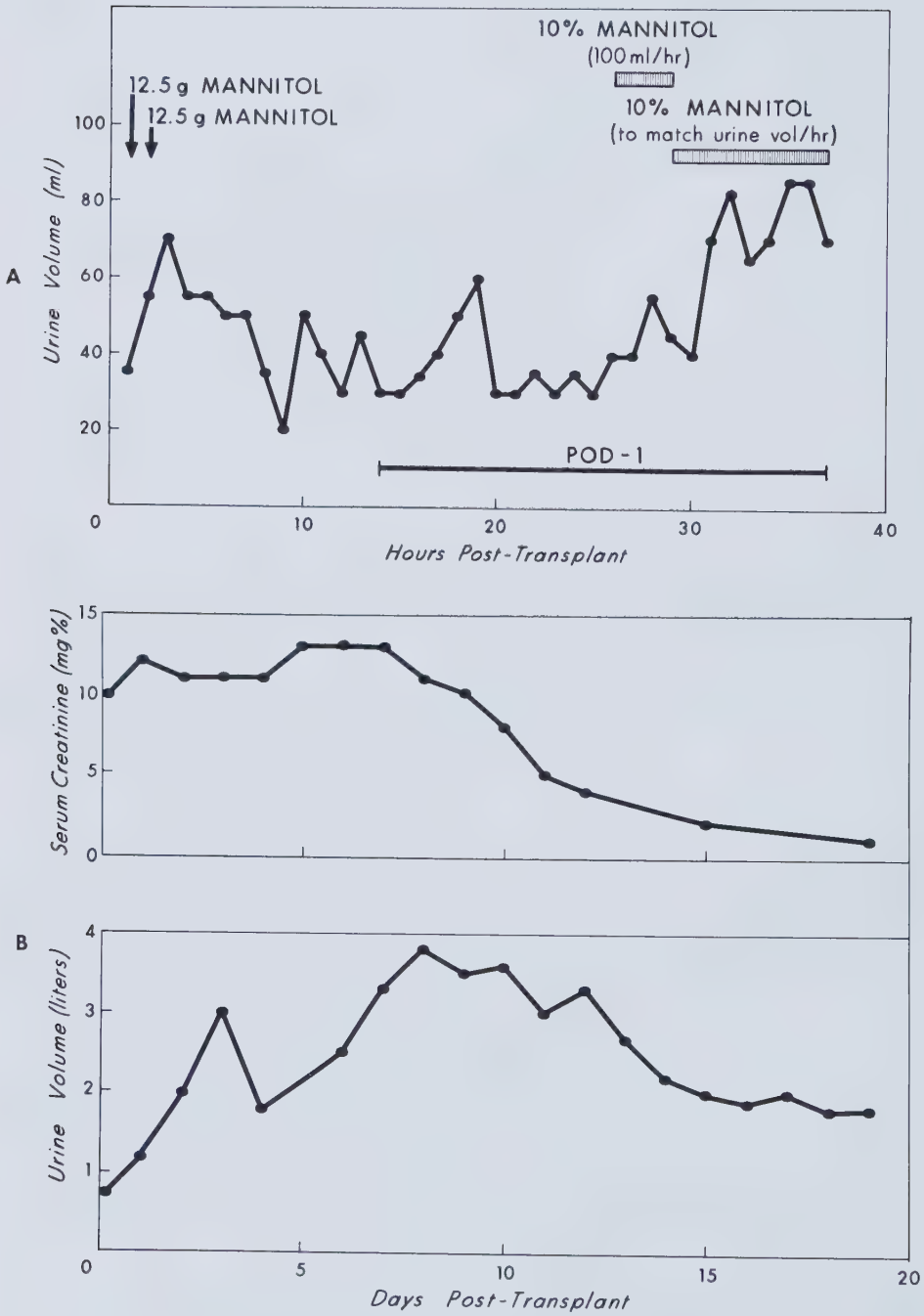

Fig. 6-10. Treatment of patient with early acute renal failure with mannitol. **A**, First 40 hr following transplant. **B**, First 20 days.

clearances of 4.6 and 6.3 ml/min. Considering the many sources of error, it would be unwise to attach too much significance to these values. However, the difference in urinary creatinine (800 and 1000 mg) was clear and significant. In the additional urine volume of day 2 there was a 20% increase in creatinine excretion. This resulted in the stabilizing of the creatinine. Fluid management was not a problem nor was potassium. The patient did not require dialysis. By day 7 renal function began steadily improving and the serum creatinine level fell until a value of 1.0 mg% was attained on day 19. Mannitol therapy in this case was associated not only with increased urine volume but also with increased creatinine excretion. This implies increased glomerular filtration.

More recent experience would suggest that furosemide may be a better agent, since it increases renal blood flow out of proportion to cardiac output,[18] whereas mannitol increases renal blood flow in proportion to increased cardiac output.[31] From 1000 to 2000 mg of furosemide/day has been used with benefit.[12] Fig. 6-11 shows data from a patient treated in this way. These data are from a 79-year-old male who had an abdominal aneurysm resected. A preoperative creatinine clearance measurement of 53 ml/min was obtained. The surgeon administered furosemide and mannitol immediately prior to clamping the aorta, but urine flow was rather low at the time the aorta was clamped. We believe this is an important point. The aorta was occluded for 38 min. After removing the clamp there was a 15 min period of hypotension. Urine flow dropped precipitiously. The patient remained severely oliguric for the ensuing 7 hr. A continuous infusion of furosemide was then instituted with the rather dramatic results shown in Fig. 6-11. Urine volume was maintained following the period shown without additional diuretic treatment. The preoperative serum creatinine

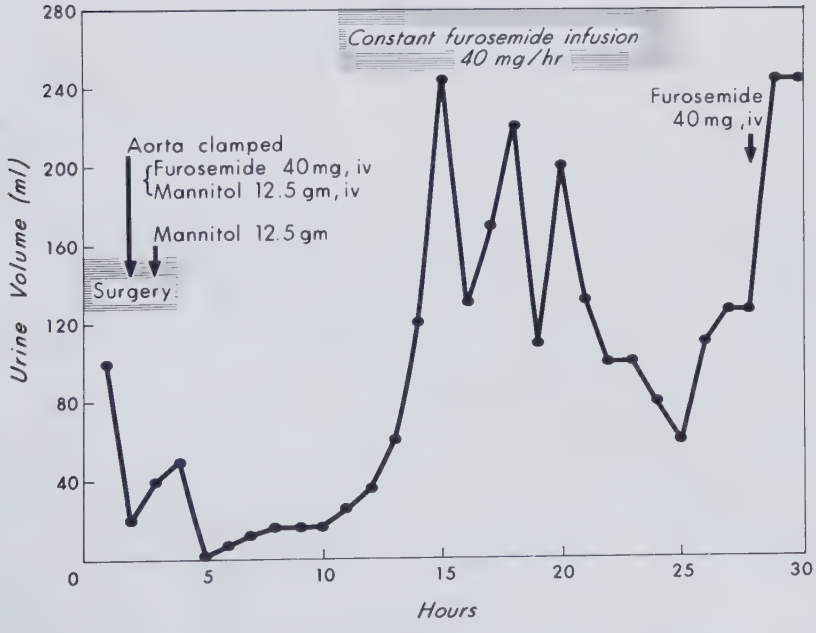

Fig. 6-11. Treatment of patient with early acute renal failure with furosemide infusion.

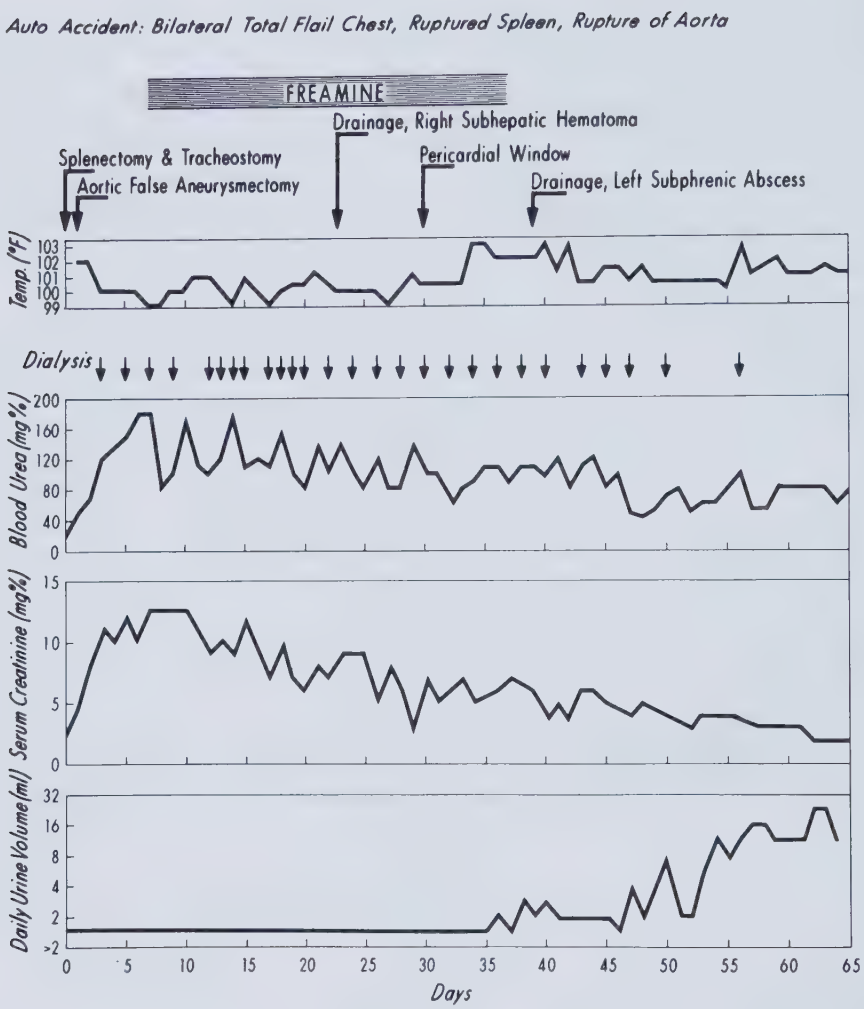

Fig. 6-12. Treatment of patient with acute organic renal failure.

level was 1.6 mg%, on the first postoperative day it was 4.9 mg%, but on the third day it was 1.8 mg%. A creatinine clearance measurement obtained on the third day was 35 ml/min, and by the fourth day it was 46 ml/min. Care should be taken not to overhydrate these patients. After the initial test of fluids along with mannitol, fluids should be administered only in relation to output.

One advantage of furosemide over mannitol in this situation is that furosemide does not expand the intravascular volume directly. Thus if no diuresis results from the therapy, the patient is not left with the expanded blood volume that can be expected with mannitol.

When an adequate urine volume can be obtained, the patient will follow a fairly predictable course. Barring major complications, the serum creatinine and blood urea levels will rise transiently until the creatinine clearance improves, and thereafter serum values will return to normal. However, serum potassium and fluid overload are not problems.

If the patient proves to have "organic" renal failure, a course of oliguria varying from several days to several weeks can be anticipated. Ready access to the circulation should be provided promptly, and dialysis should be begun very early before major derangements have developed. Fig. 6-12 illustrates the intensive dialyses required to obtain survival in such patients.

The patient whose illness is delineated in Fig. 6-12 is a young male who was severely injured in an automobile accident. He had signs of blood loss on admission and underwent splenectomy for splenic rupture. Shortly afterward the blood pressure in the left arm was noted to be lower than that in the right. An arch aortogram demonstrated a traumatic aortic rupture with a false aneurysm. This was corrected under partial cardiac bypass. Shortly after this procedure the patient became virtually anuric and remained so for 35 days. A gradual recovery of renal function followed and he was last dialyzed 56 days after injury. Note the very rapid rise in blood urea and creatinine levels in the first few days after injury; these remained at very high levels despite frequent dialysis. This is the result of the severe catabolic load associated with his injuries and operations. Note that these values gradually declined, despite less frequent dialyses, well before significant renal function developed. He was dialyzed 27 times in 56 days. Three additional surgical procedures were required, but fortunately they engendered little catabolic response and the trend to less rapid catabolism was not interrupted.

Freamine was given to lower the endogenous protein catabolism, but no real effect can be seen in this patient. The use of intravenous essential amino acids in some patients may be helpful. The use of this material is based on the minimal daily requirements of protein necessary to maintain nitrogen balance. When not provided, endogenous protein catabolism will be greater. By supplying the essential amino acids, protein catabolism is minimized. A side effect that is probably of no consequence is the decline in urea during protein synthesis from exogenous essential amino acids.[14] This appears most useful in patients with complications that result in very high catabolic rates.[1]

KIDNEY SURGERY THAT MAY PRODUCE ISCHEMIC DAMAGE

Renal vascular disease represents an area of surgery that deserves special mention. The relief of stenosis in renal arteries under usual circumstances represents no great problem. A bypass graft of autogenous vein or an endarterectomy can frequently be performed within an acceptable period of ischemia. However, in our opinion too many nephrectomies are done for more difficult technical reconstructions. More attempts at ex vivo repair with autotransplantation are indicated. Gelin et al.[17] report substantial experience in this work. A kidney can readily be removed, perfused, and maintained hypothermic. Several hours can be used for a careful reconstruction in a bloodness field. The kidney is then salvaged by autotransplanting it, usually into an extraperitoneal position in the right lower quadrant as routinely done in renal allotransplantation.

In such patients the kidney should be removed during actual diuresis. Hydration should be maintained by intravenous therapy during the preoperative starvation period. Diuresis should be maintained intraoperatively by either furosemide or mannitol. An infusion of low molecular weight dextran is preferred by Gelin et al.[17] for this purpose. The lack of arterial spasm that is often

precipitated by the vascular dissection in kidneys not treated in this way is quite impressive on gross examination.

On removal of the kidney it should be perfused with a solution of Ringer's lactate previously cooled at 4° C and containing procaine, heparin, and sodium bicarbonate. This is infused rapidly through a cannula into the renal artery until the venous effluent is clear, which renders the organ hypothermic and bloodless. The infusion can then be continued at a slow rate sufficient only to maintain hypothermia. Gauze packs soaked in cold solution may be laid on the renal surface to assist in maintaining hypothermia. Meticulous reconstruction can then be carried out in a leisurely way. The abdominal wound can be closed by assistants during this period. If the reconstruction is successful, a second incision is made in the right lower quadrant for reimplantation.

SUMMARY

Experience in the surgical care of patients with chronic renal failure has led to the recognition of important features in the surgical care of patients with all degrees of restricted renal function. This experience has been surveyed, with particular attention given to the physiologic rationale for various therapeutic measures and the maintenance of existing renal function, along with important details in the successful execution of major surgical procedures in such patients.

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7

Iatrogenic short bowel syndrome: surgical treatment of morbid exogenous obesity

LESLIE WISE

Life insurance studies clearly indicate that overweight is a major health problem among adult Americans, particularly those past midlife. These studies have also clearly shown that overweight subjects experience a significantly higher mortality than subjects of average or less than average weight and that the greater the degree of overweight, the larger the excess mortality.[77] The cumulative excess mortality over an 18-year period increased rapidly with increasing weight, and it amounted to 13% for men 10% overweight (i.e., 10% above average weight), 25% for those 20% overweight, and over 40% for those 30% overweight. The cumulative excess mortality among women was somewhat less.

The disadvantage of obesity showed up even more clearly when the mortality of overweight subjects was compared with the mortality of subjects with desirable weights (i.e., the weight groups recording the lowest mortality for given heights). Compared with the experience in the desirable weight range, men 10% or more overweight had a cumulative excess mortality of 33%, and in those who were 20% or more overweight, the excess mortality was nearly 50%. The excess mortality was chiefly due to cardiovascular disease, including cerebral hemorrhage and thrombosis; overweight, however, also carried distinctly higher rates of death from diabetes and digestive diseases such as cholelithiasis and cirrhosis.

Statistical studies also indicate that weight reduction has a favorable effect on overweight subjects.[77] It was shown that overweight men who reduced to

standard weight experienced practically the same mortality as those maintaining standard weights.

Although it is evident that many overweight people can lose weight by dieting, exercise, and other conservative means, the long-term follow-up on such persons has been generally discouraging. This is because the majority of those who initially achieve a significant weight loss tend to regain it later on. The rationale proposed for the surgical treatment of morbid exogenous obesity is twofold: (1) the well-recognized hazards of obesity and (2) the frequent long-term ineffectiveness of conservative weight reduction programs.

In 1954 Kremen et al.[39] reported that controlled resections of the small bowel resulted in impaired fat absorption and weight loss in dogs. It has also been known for a long time that massive small bowel resection in humans (usually carried out for mesenteric vascular accidents) resulted in significant weight loss, usually without loss of life.[10, 49, 82]

In 1963 Payne et al.[54] were the first to report their experience with *jejunocolostomy* for the treatment of morbid exogenous obesity (Fig. 7-1). They described the results with 10 patients in whom jejunotransverse colostomy was performed, leaving 15 to 20 inches of jejunum in continuity. Diarrhea, hypokalemia, and hypocalcemia were noted in these patients. In 1966 Lewis et al.[41] reported their experience with jejunocolostomy in 11 patients. They left 20 to 30 inches of jejunum in continuity. One of the 11 patients died suddenly on the fifth postoperative day; at autopsy the cause of death could not be determined. The most rapid weight loss occurred during the first 6 months, but loss continued for years until approximately normal weight was reached. The follow-up study period ranged from 8 months to almost 6 years. Both Payne et al.[54] and Lewis et al.[41] reported flattened glucose tolerance curves after the jejunocolic bypass. Lewis et al. also found that the dietary calorie intake of these patients was significantly reduced following the operation.

A number of others[9, 41, 44, 56, 71] have also reported their experiences with

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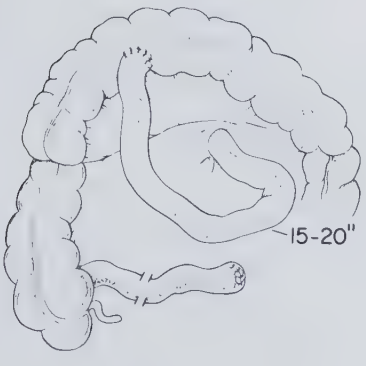

Fig. 7-1

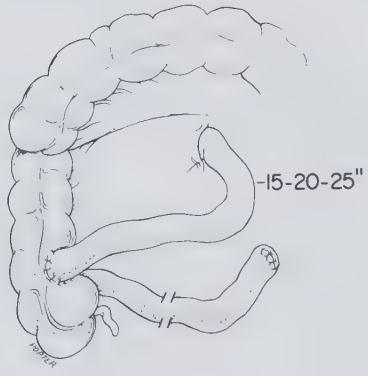

Fig. 7-2

Fig. 7-1. Jejunocolic bypass (Payne type I procedure): 15- to 20-inch end-to-side jejunotransverse colostomy.
Fig. 7-2. Jejunocolic bypass (Shibata's modification): 15- to 25-inch end-to-side jejunocecostomy.

Table 7-1. Survey of jejunocolostomy procedures

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Payne et al. (1963)[54]	10	5: 1 incisional hernia; 1 wound seroma; 2 temporary hair loss; 1 thrombophlebitis	8: 5 hypokalemia; 3 hypocalcemia	1: died 6 mo postoperatively of pulmonary embolism	52.8 wk	26-112 wk
Sherman et al. (1965)[71]	1	Prolonged severe diarrhea	Yes	No	14 mo (then revised to jejunoileostomy)	14 mo
Bondar and Pisesky (1966)[9]	7	Not stated	Apparently noted in all patients (hypocalcemia, hypokalemia, hypomagnesemia)	2: 1 hepatic coma following revision of bypass; 1 fluid retention with massive anasarca and clinical kwashiorkor	14 mo	5-22 mo
Lewis, Turnbull, and Page (1966)[41]	11	7: anorexia and nausea for few months; no other details	11: 4 hypokalemia; 4 hypocalcemia; 3 hypomagnesemia	2: one 5 days postoperatively suddenly, cause of death not determined; one 8 mo postoperatively from pulmonary embolism	2 yr, 1 mo	7 mo-5 yr, 11 mo
Kaufman and Weldon (1967)[38]	1	Intussusception of excluded segment at 2 yr, 9 mo	Not stated	No	3 yr, 9 mo	—
Shibata, MacKenzie, and Long (1967)[73]; Shibata, MacKenzie, and Huang (1971)[72]	11	4: 1 respiratory arrest due to over dosage of tincture of opium, followed 2 days later by upper GI hemorrhage, treated with	12: 4 hypocalcemia; 4 hypomagnesemia; 4 hypokalemia	1: 3 mo postoperatively of "hepatic failure"	19 mo	3 mo-3 yr, 11 mo

Median wt. loss	Liver		No. who required revision	Status at time of report	Length of functional small bowel
	Biopsy	Function			
123 lb	Followed in 9 patients: 6 increased fatty change; 3 no change	Followed in 5 patients: 2 depressed; 2 no change; 1 improved	All (i.e., 9)	5 definite weight loss; 4 not stated	15 inches, jejunum to transverse colon
214 lb	Not stated	Not stated	1	Satisfactory	15 inches, jejunum to transverse colon
82 lb	No preoperative biopsies; postoperatively fatty change in all	No preoperative studies available; postoperatively, depressed function in all	5 (remaining 2 died)	Not stated	24-36 inches, jejunum to transverse colon
141 lb	Followed in 7 patients: 2 increased fatty change; 5 no change	Followed in 5 patients: no change	2	Apparently satisfactory in 7	20-30 inches, jejunum to transverse colon
130 lb during first 6 mo and "maintained this weight"	No data	"Normal LFT's at 2 years 6 months"	None	Apparently good	"Approximately 2 feet of jejunum to cecum"
107 lb	Followed in 7 patients: 2 increased fatty change; 5 no change	Followed in 4 patients: immediate depression in all, followed by return to normal in 3 within 12 mo	3	Gain in weight in revised patients	15-25 inches, jejunum to ascending colon

Continued.

Table 7-1. Survey of jejunocolostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Shibata et al. —cont'd		V & P; 1 necrotizing tracheitis on second postoperative day, also thrombophlebitis and thinning of hair; 1 wound dehiscence, thrombophlebitis, arthritis; 1 wound infection followed by wound dehiscence				
Maxwell, Richards, and Albo (1968)[48]	1	Paralytic ileus; wound infection; gouty arthritis	No data	1: hepatic failure	119 days (i.e., 4 mo)	—
Barron, Frame, and Bozalis (1969)[6]; Shagrin, Frame, and Duncan (1971)[70]; Dickstein and Frame (1973)[19]	23	39: 1 ventral hernia; 4 internal hernias; 2 intussusception of closed portion of jejunum; 7 orthostatic hypotension; 2 gastric ulcers; 2 tetany; 5 electrolyte imbalance; 7 rheumatoid-like polyarthritis; 9 urinary calculi (During 2-7 yr follow-up period, average interval between	At least 5	2: hepatic failures 6 and 10 mo after bypass	Not stated	Up to 5 yr

Median wt. loss	Liver		No. who required revision	Status at time of report	Length of functional small bowel
	Biopsy	Function			
48 lb	No preoperative biopsy; at autopsy, "massive fatty infiltration with no evidence of cirrhosis"	Preoperatively, inadequate liver function data; prior to death, bilirubin level of 15.4 mg%	None	Dead (hepatic failure, renal failure)	15 inches, jejunum to transverse colon
100 lb during first year	No data	"Significant elevation of BSP during the first twelve months"	?4 (not clear from data)	"All patients stated that 'they would undergo the operation again under similar circumstances'"	45-50 cm, jejunum to transverse colon

Continued.

Table 7-1. Survey of jejunocolostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Barron, et al.; Shagrin et al.; Dickstein and Frame—cont'd		shunt procedure and stone formation was 1 yr, 8 mo. Range: 24 days to 6 yr.)				
Delena et al. (1970)[17]	1	Hepatomegaly with depressed liver function	Hypokalemia; hypocalcemia; hypomagnesemia	No	22 wk	—
Drenick, Simmons, and Murphy (1970)[23]	1	No data	No data	1: hepatic failure	7 mo	—
Burcher and Sorrell (1971)[15]; Sorrel and Burcher (1969)[76]	2	"Wounds were slow to heal"	Hypopotassemia; hypokalemia; hypomagnesemia (data only available for 1)	None	18 mo	18 mo
Ciongoli and Poser (1972)[16]	1	Fat malabsorption neuromyopathy	Apparently no problems	No	3½ yr	—

Median wt. loss	Liver		No. who required revision	Status at time of report	Length of functional small bowel
	Biopsy	Function			
95 lb	Fatty change (but liver biopsy not obtained at time of original surgery); 35 wk after revision, normal biopsy	No preoperative studies done; function depressed after shunt; 35 wk after revision, normal function	1: because of hepatic dysfunction	35 wk after revision gained 15 lb	26 inches, jejunum to transverse colon
130 lb	Preoperatively, moderate fatty change; 7 mo postoperatively, massive fatty infiltration with fibrous strands	No data given	None	Dead (hepatic failure)	"Less than 30 inches of small bowel remained in continuity to transverse colon"
103 lb	Marked fatty infiltration in 1; no data given on second patient	Marked depression in 1; no data given on second patient	1: 8 mo postoperatively because of rapid development of fatty liver	Now both doing reasonably well	Jejunocolostomy; length of functional jejunum not stated
180 lb in first 2 yr	Inadequate data	Inadequate data	Reconverted 3½ yr postoperatively because of fat malabsorption neuromyopathy	Apparently satisfactory	24 inches jejunum to transverse colon

this procedure. Shibata et al.[72] modified the operation from jejunotransverse colostomy to jejunocecostomy (Fig. 7-2).

Many of the patients with jejunocolostomy had significant problems with diarrhea, electrolyte depletion, and liver failure. With severe diarrhea, water and protein are lost in combination with sodium, potassium, calcium, magnesium, bicarbonate. and chloride ions. A not uncommon manifestation is metabolic acidosis with hypokalemia. With prolonged diarrhea hypocalcemia and hypomagnesemia may also occur. A low serum potassium usually indicates a considerable deficit, but a normal value does not exclude a deficit, since the extracellular fluid compartment represents only 2% of the total body potassium stores, while the remaining 98% is located in the intracellular compartment. The most common clinical manifestation of hypokalemia following bypass procedures is muscle weakness. Gross potassium loss may also have important secondary effects on renal tubular function. Hypocalcemia may lead to tingling and numbness of the extremities; in more severe cases, painful cramps of the hands and feet may also occur. Adduction of the thumbs together with plantar flexion of the feet constitutes the so-called carpopedal spasm. Prolonged hypocalcemia may lead to osteomalacia and cataracts. The published results of jejunocolostomies for morbid obesity are summarized in Tables 7-1 and 7-2.

In 1963 Wood and Chremos[88] reported their results in a patient with a *jejunoileostomy.* They noted excessive steatorrhea without weight loss. In 1969 Payne and DeWind[53] described their experience with a modified small bowel bypass in which the integrity of the ileocecal valve was maintained (Fig. 7-3). This procedure consisted of dividing the jejunum 14 inches from the ligament of Treitz and anastomosing this segment end-to-side to the terminal ileum, 4 inches from the ileocecal valve. In an experience with 70 patients they have found this a fairly satisfactory procedure, although they noted the development of hepatomegaly and fatty infiltration of the liver in some of the patients. They cautioned that the operation "should definitely be considered as an investigative procedure for the present and should not be undertaken unless facilities are available to handle complications and to conduct significant research into the mechanism of obesity and its attendant complications over a long period of time."

In 1969 Scott and Law[67] also reported their experiences in five patients with a modified Payne procedure. In later studies from Scott's group,[11, 68] it was reported that 5 of 11 patients with the 14/4 Payne operation failed to lose adequate amounts of weight. Upper gastrointestinal studies of possible causes of failure in these patients have shown dilatation and elongation of the proximal jejunum and terminal ileum, with reflux of barium into the bypassed ileum for

Table 7-2. Summary of jejunocolostomy studies

Number of reported cases	70
Mortality	11 (15.7%)
Hepatic failure	8
Pulmonary embolism	2
Cardiac arrhythmia	1
Number of revisions	25/59 (42%)

distances of 3 to 5 feet. All of the 11 patients had problems with diarrhea during the first 3 months, but this gradually improved. Every patient had severe steatorrhea with resultant fall in serum carotene and cholesterol levels. As measured by the D-xylose tolerance test, a significant reduction in carbohydrate absorption occurred in 1 of the 11 patients. Three of the 11 patients developed hepatomegaly with fatty liver 6 to 12 months after the bypass. The cause of this is unknown. Dragstedt[22] suggested that the fatty metamorphosis following bypass surgery was a result of dietary deficiency, perhaps of choline and methionine or lipocaic.

In 1971 Scott et al.[69] reported their experience with a new bypass in 12 patients (Fig. 7-4). They used a 12/12-inch end-to-end jejunoileal bypass; the excluded small bowel was anastomosed end-to-side to the transverse or sigmoid colon. Only a 6-month follow-up study was available, and at that stage the results seemed fairly satisfactory. There are numerous other reports on jejuno-

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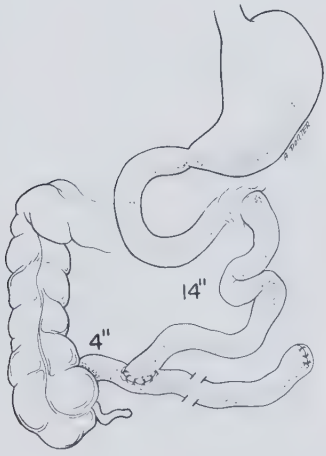

Fig. 7-3. Jejunoileal bypass (Payne type II procedure).

Fig. 7-4. Jejunoileal bypass (Scott procedure). Bypassed segment of small bowel is anastomosed end-to-side either to transverse or sigmoid colon.

Table 7-3. Survey of jejunoileostomy procedures

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Payne, DeWind, and Commons (1963)[54]; Payne and DeWind (1969)[53]; Payne et al. (1973)[55]	153: 140 of these were 14/4 type; others were similar type but of various lengths	Discussed in 1963 and 1969 articles; recalculations show that of 70 patients with jejunoileal shunts, 58 were 14/4 and 12 had jejunal lengths of 15-20 inches and ileal lengths of 5-20 inches; 4 deaths occurred (2 myocardial infarcts, 1 pulmonary embolism, 1 hepatic failure); 10 other complications developed (1 seroma, 2 skin necrosis, 2 hernias, 1 wound infection, 1 bowel obstruction, 2 intussusception, 1 gastric ulcer hemorrhage)	"Most patients require potassium supplementation"; no details given	15: 5 hepatic failure; 2 pulmonary embolism; 3 cardiac failure; 1 electrolyte imbalance; 1 hemorrhagic pancreatitis; 1 alcoholic liver failure; 1 cholelithiasis and liver failure; 1 Thorazine intoxication (NOTE: Mortality related to bypass; 15/153 = 9.8% [recalculated].)	Not stated	Up to 16 yr
Wood and Chremos (1963)[88]	1	"3 to 4 foul smelling stools daily" and failure to achieve weight loss	No	No	2 yr, 6 mo	—
DeMuth and Rottenstein (1964)[18]	1	Death	Hypocalcemia	1: 8 mo postoperatively from hypocalcemia	8 mo	—

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
First 6 mo, 10.9 lb/mo; second 6 mo, 6 lb/mo; second yr, 4.6 lb/mo; third year, 2.2 lb/mo; fourth year, 0.75 lb/mo	Sequential biopsy specimens in 36 patients; no details published (IMPRESSION OF AUTHORS: "During weight reduction, fatty infiltration increases. The development of fibrosis can be anticipated in the presence of malnutrition and alcohol ingestion. After initial weight loss there is an improvement in liver histology.")	Not stated	4 required complete revision to normal because of inability to maintain electrolyte balance except in hospital or because of alarming changes in liver function tests; 16 required revision because of failure to lose an appropriate amount of weight, partly because of elongation of jejunum; 12 required further resection of jejunum; 4 converted to 14/4 end-to-end anastomosis	Difficult to establish	Most commonly end-to-side	Most commonly 14 inches	Most commonly 4 inches
None (4 lb weight gain)	Not done	Not stated	None	Foul-smelling stools so distressing she has confined herself to home	End-to-end	18 inches	8 inches
69 lb in 7 mo	No good data	No good data	None	Dead	End-to-side	26 cm	13 cm

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Troncelliti (1966)[80] (1972)[81]	53	No data	No data	8	No data	No data
Morgan and Moore (1967)[51]	1	None	Supplementary calcium, potassium, and magnesium given	No	3 yr	—
Maxwell, Richards, and Albo (1968)[48]	1	Immediate complications not stated Late complications: intussusception of excluded jejunal stump requiring reoperation 4 mo postoperatively and hepatic failure that required reanastomosis	Hypocalcemia; no further details	No	6 mo	—
Barron, Frame, and Bozalis (1969)[6]; Shagrin, Frame, and Duncan (1971)[70]	9	? None; no evidence of polyarthritis	Yes; no details given	Not stated	Not stated	Not stated
Jensen (1969)[35]	2	2: 1 subcutaneous infection; 1 pneumonia (same patient)	2: 1 hypokalemia, 1 hypocalcemia; hypomagnesemia in both	None	13 mo	10-16 mo

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
No data	No data	No data	No data	No data	End-to-side	15-18 inches	3-5 inches
66 lb loss during first year; no further loss since then	No data	No data	None	Doing well	End-to-side	15 inches	10 inches
Not stated	No preoperative biopsy: 6 mo postoperatively, extensive fatty change	No preoperative data; 6 mo postoperatively, bilirubin, 2.4, and albumin, 2.1; i.e., hepatic failure	1 (intestine hooked back to normal)	Satisfactory	End-to-side	10 inches	10 inches
86 lb during first year	Not done	"Significant elevation of BSP during the first 12 mo with the peak about 6 mo postoperatively. By 16 mo in most pt. the BSP returned to normal"	?None	"All patients stated that they would undergo the operation again under similar circumstances."	End-to-side	14 inches	4 inches
83 lb	Not done	Abnormal prothrombin level in 1; alkaline phosphatase and SGOT remained unchanged from preoperative levels	None	Good	End-to-side	36 cm	12 cm

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Wills (1969)[87] (1967)[86]	50	23: 5 wound infection; 1 evisceration; 1 seroma; 2 atelectasis; 7 ventral hernias; 1 intractable diarrhea and intolerable stool odor (This patient insisted on and received reestablishment of bowel continuity 5 mo postoperatively. She quickly regained her original weight.); 1 recurring attacks of fever, headache, and vomiting and nephrocalcinosis 1 yr postoperatively (continuity reestablished); 3 intussusception of blind jejunal loop; 1 acute GI hemorrhage of undetermined cause; 1 ascending cholangitis 4 days postoperatively	"22 cases had clinical and laboratory evidence of serum potassium and calcium deficiencies. Obviously additional mild deficiencies occurred without recognition."	At least 2: 1 pulmonary embolus 24 days postoperatively; 1 bleeding esophageal varices (? date)	18.4 mo	5-32 mo

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
71 lb	No sufficient data	No sufficient data	3	No good data	End-to-side (Payne II)	14 inches	4 inches

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Drenick, Simmons, and Murphy (1970)[23]	2	No data	No data	None	9½ mo	6-13 mo
Scott and Law 1970)[67]; Scott et al. (1970)[68]	11	11: 3 major subcutaneous infections requiring drainage; low-grade fever in each patient (11), possibly pulmonary in origin	No hypocalcemia; 4 mild hypomagnesemia	None	18 mo	5-36 mo
Tanga, Waddell, and Wellington (1970)[78]	1	Jejunoileal intussusception 8 mo postoperatively; immediate complications not stated	No data	No	8 mo	—

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
115 lb (in 1 patient in 13 mo; no data on other patient)	In 1 preoperatively, fatty changes; 13 mo postoperatively, massive centrilobular fatty degeneration; no preoperative biopsy in other patient; 6 mo postoperatively, fatty degeneration with fibrosis	1 essentially normal, except for elevated BSP (9%); 1 bilirubin level 1.9, no BSP done	Not stated	Not stated	"Less than 30 inches of small bowel in continuity"		
96 lb	3 hepatomegaly and marked fatty metamorphosis 6-12 mo postoperatively; no biopsy data in others	Abnormal in 3 with hepatomegaly	None	Good	End-to-side (Payne II)	14 inches	4 inches
Approximately 100 lb	No data	Liver function depressed	1 revised at time of laparotomy for intussusception; because of rapid weight loss and liver dysfunction, 15-inch small bowel inserted in an isoperistaltic fashion in functioning loop	Satisfactory	End-to-end	15 inches	10 inches

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Thompson and Meyerowitz (1970)[79]; Meyerowitz (1971)[49]	29	Not stated	Not stated	Apparently none	Not stated	"25 patients followed for one year or more"
Baddeley (1971)[3, 4]	4	None	None	None	8.2 mo	4-18 mo
Burcher and Sorrell (1971)[15]	3	1: deep vein thrombosis	"Signs of electrolyte depletion"	None	8 mo (data on only 2 patients)	7-9 mo (data on only 2 patients)
Schwartz, Varco, and Buchwald (1972)[66]; Buchwald and Varco (1971)[14]	84	27: 2 superficial thrombophlebitis; 1 pneumonia; 2 pulmonary emboli; 4 upper GI bleeding; 10 sterile serolipid drainage from wound; 2 gross wound infection; 6 urinary tract infection	"Electrolyte balance maintained by oral supplementation"	1: "perforated stress ulcer of colon"	Not stated	Up to 2 yr

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
"The majority had impressive weight reduction"	24 of 25 had some fatty infiltration at time of shunt; 12 had repeated biopsies, 15-18 mo postoperatively (Results: 7 improvement, 4 deterioration, 1 no change)	Biochemical tests generally showed improvement after bypass	Not stated; at least 1 had conversion to end-to-end[79]	3 "complete failures" (? no weight loss)	End-to-side	14 inches	4 inches
60 lb	Not stated	Not stated	None	All satisfied	End-to-side	14 inches	4 inches
68 lb (data on only 2 patients)	Moderate fatty infiltration preoperatively; unchanged at 4 and 8 mo postoperatively	"No signs of deterioration of liver function"	None	1 well; 1 not happy because of occasional episodes of incontinence; 1 developed cerebral glioma	End-to-side	14 inches	4 inches
Not stated	Not stated	Not stated	None	Not stated	End-to-end	40 cm	4 cm

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Juhl et al. (1971)[36]; Quaade et al. (1971)[59]; Baden et al. (1969)[5]	10	No complications in first 8; results with last 2 not stated	Some hypokalemia and hypomagnesemia, but no severe problems	None	21.4 mo	12-27 mo
Salmon (1971)[63]	120	Not stated	"49% no abnormality anytime during the study. 41% had a detectable abnormality in potassium or calcium or both"; 10% not stated	5: 4 wound evisceration complicated by infection (1 of these also had associated intestinal obstruction and leak at ileocolonic anastomosis); 1 massive pulmonary embolus (operative mortality rate: 4%)	Not stated	6 mo-3½ yr

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
86 lb	7 had both intraoperative and postoperative biopsies 10-27 mo postoperatively, showing fatty infiltration (3 increased, 3 decreased, 1 no change)	LFT's showed transient deterioration for few months postoperatively, but later improved as compared to mean preoperative values	None	Apparently all satisfactory	End-to-side	37 cm	12 cm
"At the time the results were compiled, 63% of the patients operated upon were not more than 20 lbs above ideal weight"	Preoperative biopsies in 33 patients showed 61% with some degree of fatty infiltration; 47 follow-up biopsies (IMPRESSION OF AUTHOR: "Some degree of fatty infiltration develops in almost all patients. Subsequent to rapid weight loss fat seems to disappear slowly from the liver" [no hard data given])	No hard data given	Not stated; ?none	"All patients have returned to previous employment."	End-to-end; excluded segment anastomosed to transverse colon	10 inches	20 inches

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Scott et al. (1971)[69]	12	12: 3 subcutaneous wound infections requiring drainage; 1 urinary tract infection; low-grade fever in each patient (12), possibly pulmonary in origin	No hypocalcemia; no hypomagnesemia in 8 patients studied; no hypokalemia	None	5.6 mo	1-12 mo
Shibata, MacKenzie, and Huang (1971)[72]	3	1: jejunojejunal intussusception in blind segment	1: hypocalcemia, hypokalemia, and hypomagnesemia	None	43 mo	34 mo-4 yr
McGill et al. (1972)[43]	1	Hepatic failure	Not stated	Yes; hepatic failure	1 yr, 1 mo	—

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
45 lb	No data	No data	None	11 pleased with result; 1 unhappy (only 28 lb loss in 12 mo period; this patient had 18-inch segment of jejunum)	End-to-end	12 inches	12 inches
130 lb in 2 yr	1 showed 50% fatty infiltration preoperatively and only 25% 3 yr later; 1 showed 75% fatty infiltration preoperatively and only 25% 3 yr later; 1 converted to jejunocolostomy and no biopsy taken at time of conversion	All 3 normal preoperatively; postoperatively, 1 normal, 1 finally normal after being abnormal immediately postoperatively but returned to normal within about 9 mo, 1 abnormal with bilirubin increased at time of conversion	1 patient after failure to lose sufficient weight over 2 yr period was converted to jejunocolic bypass, but subsequently required restoration of small bowel continuity	No data on 1; 1 lost weight, from 330 to 160 lb, finally weighing 200 lb; 1 apparently doing well	End-to-side	15 inches	5 inches
127 lb	Moderate fatty infiltration preoperatively; at autopsy, cirrhosis with postnecrotic features	Normal preoperatively, bilirubin 8 mg% just prior to conversion back to normal	1 conversion 6 days prior to death (because of liver failure)	Died	End-to-side (Payne II)	14 inches	4 inches

Continued.

Table 7-3. Survey of jejunoileostomy procedures—cont'd

Author	No. of patients	No. and types of surgical complications	Electrolyte disturbances	Died as result of surgery	Shunt period	
					Median time	Range
Dickstein and Frame (1973)[19]	11	2: developed urinary calculi during a 2-7 yr follow-up period	No data	No data	No adequate data	No adequate data
Randhawa et al. (1973)[60]	17	2: jaundice with impending hepatic coma	No data	No data	No data	No data
Weisman (1973)[85]	123	17: 6 wound infection; 2 hepatitis ("drug" or "anesthesia"); 1 dermatitis ("drug"); 2 thrombophlebitis; 2 pulmonary embolism Late complications: 3 incisional hernias; 1 intussusception of jejunum 6 mo postoperatively	"Potassium supplementation required in only 3 patients"; no details given about calcium and magnesium	3: 2 pulmonary embolism (days 4 and 17); 1 liver necrosis 6 mo postoperatively	1.5 yr	2 mo-7 yr

Median wt. loss	Liver		No. who required revision	Status at time of report	Nature of operation		
	Biopsy	Function			Type	Jejunal length	Ileal length
Average of 85 lb during first year	No data	No data	No data	No data	End-to-side	Not stated	8-10 cm
No data	"5 pts developed liver dysfunction; 2 of these were jaundiced with impending coma. Except for one patient, the other 4 pt 1 yr later have normal LFT's. This demonstrates the reversibility of liver changes."		No data	No data	No data	No data	No data
Approximately 130 lb	70% had preoperative fatty infiltration of varying degree; 40 patients had both pre- and postoperative biopsies; general pattern of increasing infiltration between 6 and 12 mo postoperatively and then decrease or clearing 12-24 mo postoperatively	LFT's showed similar pattern to those of biopsies postoperatively	7: 1 had 15/10 anastomosis because of severe vomiting and malnutrition was reanastomosed about 1 yr postoperatively; 1 had 15/5, reanastomosed because of development of ulcerative colitis; 5 required revision because of inadequate weight loss	Apparently satisfactory	121: Payne end-to-side; 2: end-to-end	Varied from 12-25 inches	Varied from 4-10 inches

Table 7-4. Summary of jejunoileostomy studies

Number of reported cases	702	
Mortality	At least 36	(5.1%)
Hepatic failure	10	
Pulmonary embolism	6	
Wound evisceration complicated by infection	4	
Cardiac failure	3	
Hypocalcemia	1	
Electrolyte imbalance	1	
Bleeding esophageal varices	1	
Perforated stress ulcer of colon	1	
Hemorrhagic pancreatitis	1	
No adequate data	8	
Number of revisions	At least 34	(4.9%)

ileal bypasses (Tables 7-3 and 7-4), and the results are significantly better than those of jejunocolostomies.

The operation I am performing at present is a modification of the Scott procedure and is represented diagrammatically in Fig. 7-5. I have performed 95 of these bypasses with no operative mortality. There were two late deaths, both following revision of the bypass; the immediate cause of death in one case was hepatic failure and in the other it was a massive pulmonary embolus. Further data on these patients will be published in a later communication. In the procedure I utilize, approximately the same amount of jejunum and ileum is used as in the Payne type II bypass, but the excluded segment is anastomosed to the cecum instead of the terminal ileum. One of the problems with small bowel bypasses is the failure to lose adequate amounts of weight. This is possibly partly due to the reabsorption of nutrient chyme by reflux into the excluded small bowel segment. In my procedure I anastomose the excluded segment of small bowel to the cecum, so as to maximize the water and electrolyte absorption from the excluded segment by the colon (and so decrease diarrhea) and to minimize the reflux of intestinal chyme into the bypassed segment (presumably the intraluminal pressure in the cecum is less than the intraluminal pressure in the terminal ileum in the presence of a competent ileocecal valve). In addition, it is not unreasonable to assume that with my procedure colonic bacteria will invade at least the distal parts of the excluded segment. This bacterial colonization is likely to interfere with the absorption and utilization of nutrients.[24]

Mason and various associates[29, 45, 46, 58] use a totally different approach, a gastric bypass, for the surgical management of massive exogenous obesity (Fig. 7-6). The operation is similar to a Billroth II gastric resection except that nothing is removed. A 10% to 30% fundic segment is anastomosed to the upper jejunum and the distal segment of stomach is closed. Printen and Mason[58] recently reviewed their results with 130 gastric bypass operations and 56 gastroplasties performed for severe exogenous obesity. Gastroplasty (Fig. 7-7) maintains gastric continuity through a 1 to 1.5 cm greater curvature tube. This provides a small proximal stomach pouch as a reservoir, which empties slowly through a narrow outlet. While both gastric bypass and gastroplasty were ef-

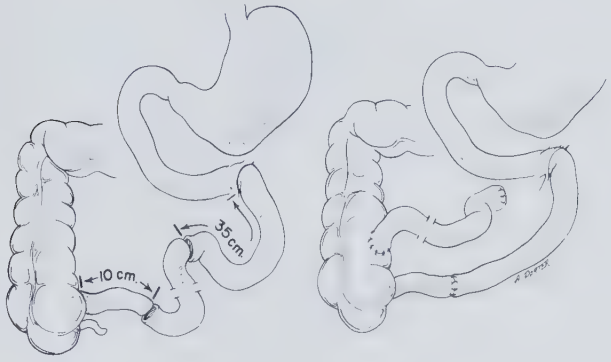

Fig. 7-5. Jejunoileostomy (Wise procedure).

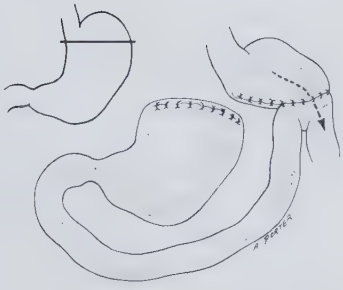

Fig. 7-6

Fig. 7-7

Fig. 7-6. Gastric bypass (Mason procedure). From 10% to 30% of fundic segment of stomach is anastomosed to proximal jejunal loop.
Fig. 7-7. Gastroplasty (Mason procedure).

fective in producing weight loss, gastric bypass was associated with more progressive and sustained weight reduction. Overall mortality was 4.6% for gastric bypass and 2% for gastroplasty. The complications of these procedures are summarized in Table 7-5.[58]

CLINICAL COURSE FOLLOWING JEJUNOILEAL BYPASS

The clinical course of patients following jejunoileostomy (Fig. 7-5) for massive exogenous obesity can be arbitrarily divided into three stages.

Phase I covers the immediate postoperative period. It has been stated that after 80% to 90% of small bowel resections, a life-threatening diarrhea often develops with the first attempt to feed such patients.[59] This certainly has not been my experience. Following bypass, the patients are treated by intravenous therapy and nasogastric suction for 3 days. During this time they have at least a partial paralytic ileus and they do not open their bowels. Their intravenous therapy consists of normal saline solution and dextrose and water supplemented by potassium. Because of the removal of hydrogen ions from the stomach by nasogastric suction, there is a tendency for the development of a metabolic alkalosis. Therefore care must be taken not to give intravenous fluids such as

Table 7-5. Complications following gastric surgery for obesity*

Complication	Gastric bypass (130 patients)	Gastroplasty (56 patients)
Wound infection	9	3
Dehiscence	2	2
Stomal obstruction	1	6
Reexploration to revise stoma	7	4
Pneumonia	1	0
Anastomotic leak	1	0
Died as result of surgery	3 (pulmonary embolus) 3 (cardiac causes)	1 (gastrostomy leak)

*From Printen, K. J., and Mason, E. E.: Arch. Surg. 106:428, 1973.

Ringer's lactate at this stage because it would predispose the patient to alkalosis. Patients usually first pass flatus on the third postoperative day, and their diarrhea begins on the fourth day. This diarrhea usually consists of 8 to 12 bowel movements a day; they are watery and the volume often exceeds 2 L/day. At this stage these patients are begun on oral fluids; usually no further intravenous alimentation is required. There is a significant loss of sodium and potassium in the diarrheal fluid, and if severe diarrhea continues, oral potassium supplements may have to be given. On the fifth postoperative day the oral intake is advanced to a low fat (40 Gm/day), high protein diet. If the severe diarrhea persists for more than 2 to 3 days with over 8 bowel actions a day, then Lomotil (5 mg qid) is prescribed. In more severe cases, codeine (30 mg qid) may have to be given temporarily to decrease the diarrheal loss. Most patients leave the hospital on the tenth postoperative day.

Phase II is the period of weight loss. This period lasts for approximately 2 years. This is also the time when various metabolic and other problems may arise, which will be discussed later.

Phase III is the final stabilizing period, and it is reached when adaptation of the remaining intestine reaches its maximum.

NORMAL DIGESTION AND ABSORPTION

To have a better understanding of the clinical problems associated with small bowel bypass procedures, the principles of normal digestion and absorption will be summarized.

Fat digestion and absorption (Fig. 7-8)

The usual amount of fat ingested in the diet ranges from 75 to 150 Gm/day and practically all of it is absorbed. Normal fat absorption is approximately 50% completed in the duodenum and 95% completed in the first 3 feet of jejunum.

Dietary lipids for the most part consist of triglycerides, which are esters of glycerol and three long-chain fatty acids. These triglycerides are insoluble in water. Pancreatic lipase is water soluble and can only act on fat globules at their interface with water. *Emulsification* of the water-insoluble triglycerides takes place in the duodenum with the dispersion of the fat into small lipid droplets. Emulsification is due to the detergent action of bile salts and fatty acids.

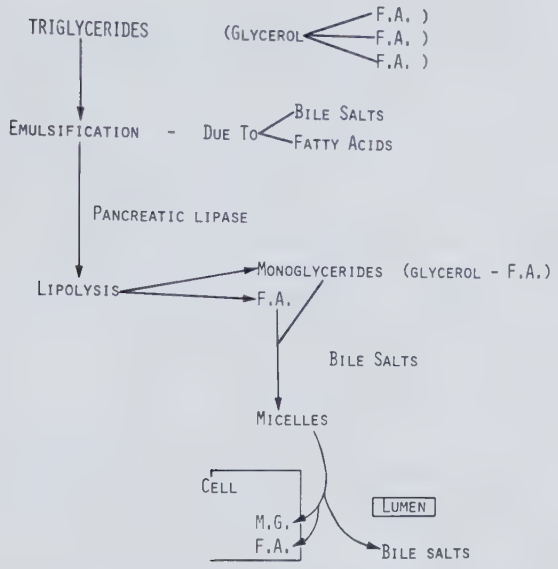

Fig. 7-8. Fat digestion and absorption. F.A. = fatty acid. M.G. = monoglyceride.

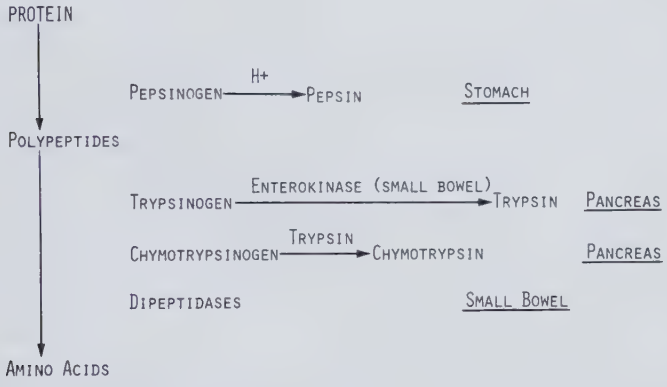

Fig. 7-9. Protein digestion and absorption.

Following emulsification, *pancreatic lipase* liberates the fatty acids from the first and third carbon atoms of glycerol, thereby accomplishing the *lipolytic phase* of fat digestion. Bile salts then combine with monoglycerides and fatty acids to form micelles (solubilization). The micellar form permits the monoglycerides and fatty acids to enter the cells; the bile salts themselves are not absorbed actively in this process and continue down the small bowel to be absorbed in the distal ileum. In the distal ileum, virtually all of the bile salts are absorbed, returned to the liver, and recirculated several times during the course of each day. This is the so-called enterohepatic circulation of bile salts.

It should be quite clear therefore that bile salts are essential for fat digestion and absorption. Following distal ileal resection or bypass, severe fat malabsorption will occur.

Protein digestion and absorption (Fig. 7-9)

Protein digestion begins in the stomach where pepsins, liberated from their precursor pepsinogens, break some of the peptide linkages. Trypsin, the main proteolytic enzyme of the pancreas, is secreted as trypsinogen, which is inactive. The intestinal secretions contain the enzyme enterokinase that splits a polypeptide from trypsinogen to form the active trypsin. Chymotrypsin is another proteolytic enzyme secreted in an inactive form by the pancreas; it is activated by trypsin. Almost all the protein is absorbed in the form of amino acids; absorption is most rapid in the duodenum and jejunum. Deficiency of dipeptidases and enterokinase may follow massive small bowel resection or bypass.

Carbohydrate digestion and absorption

The splitting of starch into the disaccharide maltose (glucose-glucose) is mainly achieved by salivary and pancreatic amylase. Salivary amylase has an optimum pH of 6.0 to 7.0 and is inactivated by the acid gastric juice; some of the enzyme, however, is engulfed in food and escapes inactivation. The disaccharides lactose (milk sugar, galactose-glucose) and sucrose (table sugar, fructose-glucose) are also ingested, along with the monosaccharides glucose and fructose. The disaccharides are hydrolyzed by lactase, sucrase, and maltase, which are located on the brush border surface of the small intestinal mucosal cells. Glucose and galactose are absorbed by active transport, and the mechanism interacts with sodium transport. The presence of sodium facilitates glucose absorption, and conversely, glucose facilitates sodium absorption. The duodenum and jejunum have the maximal capacity to absorb glucose. The rate of fructose absorption is intermediate between glucose and xylose. Xylose absorption, although slow, cannot be entirely explained by passive diffusion, and therefore it may have some active component. The term "facilitated diffusion" is applied to its absorption. Apart from occasional disaccharidase deficiencies, there are usually no major problems with carbohydrate digestion and absorption following small bowel bypass procedures for massive exogenous obesity.

Vitamins

Absorption of the water-soluble vitamins B and C is rapid. Absorption of the fat-soluble vitamins A, D, E, and K is slow if fat absorption is depressed. The vitamins are absorbed in the proximal small intestine, except B_{12}, which is absorbed in the terminal ileum.

Water, electrolytes, and trace elements

The maximum absorption of water occurs in the midjejunum; however, the colon has also a good water-absorbing capacity. As for the trace elements, both the small bowel and the colon can absorb sodium. Potassium is absorbed throughout the small intestine. The main site of absorption of chloride is the ileum. Calcium absorption takes place mainly in the proximal jejunum as an active process. Vitamin D enhances calcium absorption. Iron absorption is an active process and takes place mainly in the duodenum and to some extent in the proximal jejunum. Vitamin C facilitates iron absorption. There is evidence that calcium and magnesium compete for a common transport mechanism.

COMPLICATIONS OF SMALL BOWEL BYPASS PROCEDURES

Only the complications fairly specific to this operation will be discussed. They can be arbitrarily divided into early and late complications.

Early postoperative complications

Pulmonary problems. Respiratory failure has been reported in certain obese subjects even without surgery, producing the obesity-hypoventilation or pickwickian syndrome. It is generally accepted that increased mass loading of the ventilatory apparatus (chest wall and lungs) plays a role in the genesis of respiratory failure by causing either an insurmountable load to the respiratory muscles or significant ventilation/perfusion inequalities.[7] Other factors, however, must also be important, since not all subjects with unusually large body weight have respiratory failure, and reduction in weight is not always accompanied by a parallel improvement of the failure. In addition, although hypoxemia, as evidenced by a reduced arterial O_2 tension, is present in most obese subjects, it is not always accompanied by hypoventilation, as evidenced by an increase in arterial CO_2 tension.[34, 61]

Limited studies on markedly obese patients have been performed by Holley.[34] These findings revealed a significant ventilation/perfusion abnormality on a regional basis in obese subjects, this abnormality bearing a close relationship to the reduction in expiratory reserve volume (ERV). The etiology of this reduction in ERV has not been elucidated.

There are many reports of sudden deaths in the immediate postoperative period, when the cause is attributed to pulmonary embolus.[41, 55, 63, 85, 87] Some of these deaths may in fact have been due to cardiac arrhythmias following hypoxemia. Vaughan and I[82] have shown in 20 adults undergoing jejunoileal bypass for morbid exogenous obesity that preoperatively there was a significant reduction in their arterial O_2 tension, mean of 75.1 ± 11.1 mm Hg as against 92.4 ± 4.0 mm Hg in control patients matched for age. There was also a difference in the slope of the regression equation of P_{aO_2} vs age; the regression coefficient being significantly greater in the obese group (0.9 vs 0.46). Postoperatively there was further fall in P_{aO_2}. Decrease in mean P_{aO_2} in the obese group averaged –10.4 mm Hg 2 hr postoperatively ($p < 0.001$), –16.6 on day 1 ($p < 0.001$), –17.2 on day 2 ($p < 0.001$), –13.3 on day 3 ($p < 0.001$), and –6.7 on day 4 ($p < 0.01$). P_{aCO_2} was significantly increased above the preoperative control on postoperative days 2 (3.2 mm Hg [$p < 0.05$]), 3 (3.7 mm Hg [$p < 0.01$]), and 5 (2.8 mm Hg [$p < 0.05$]). Base excess was elevated on days 2, 3, and 4, measuring 3.7 ($p < 0.001$), 4.2 ($p < 0.001$), and 2.5 mEq/L ($p < 0.05$), respectively. Our findings indicate that in obese patients (1) preoperatively the fall in P_{aO_2} with increasing age is greater than in control subjects; (2) starting with a low basal P_{aO_2}, during postoperative days 1 through 4, the fall in C_{aO_2} often reaches dangerous levels; and (3) elevation of blood buffer on days 2, 3, and 4 can further depress respiration at a time when the P_{aO_2} has been shown to be at its lowest levels. This hypoventilation due to metabolic alkalosis can further accentuate the already existent hypoxemia. Because of these findings, we suggest careful monitoring of arterial blood gases in obese patients and the administration of O_2 and appropriate electrolyte solutions postoperatively to reduce the increased morbidity and mortality.

Wound infection and wound dehiscence. Wound infection and dehiscence are more common in the obese. The infection may partly be caused by the large volume of relatively avascular subcutaneous fat. The tension effect of the weight of heavy fat pads can contribute to dehiscence.

Diarrhea. Diarrhea may result in any of the following conditions:

1. Dehydration. This in fact is not common because most patients compensate for the diarrheal loss by extra fluid intake. There is a vicious cycle, however, because if these patients drink excessive amounts of water, then their diarrhea increases.
2. Hypokalemia and/or hypomagnesemia. Both hypokalemia and hypomagnesemia may occur due to excessive fecal loss. Like calcium, approximately one third of magnesium is bound to plasma protein; therefore both plasma calcium and magnesium levels depend on plasma protein concentration. Potassium and magnesium metabolism are closely interrelated, and in the presence of a magnesium deficit, hypokalemia is often refractory to potassium replacement. Conversely, following the administration of magnesium, there may be a sudden fall in plasma potassium levels as a result of an intracellular flux of potassium.
3. Hypocalcemia. Tetanic manifestations[73] and even death[18] related to hypocalcemia have been described. A deficiency in vitamin D absorption and possible chelation of calcium by unabsorbed fatty acids are responsible for calcium malabsorption and the occasional low serum calcium levels in patients with small bowel bypass.
4. Metabolic acidosis. This is due to loss of alkaline diarrheal fluids.
5. Perianal excoriation. This is due to the irritating action of frequent loose stools.

The etiology of the diarrhea is multifactorial. The possible causes include the following:

1. Decreased transit time and decreased surface area for absorption.
2. Fat malabsorption, which is due to bile salt deficiency, resulting in steatorrhea.
3. Bile acid diarrhea. This is probably an important factor early after operation. Normally, bile acids are absorbed in the terminal ileum by a specific process. If the terminal ileum is resected or excluded, bile salts enter the colon where they act as irritants, causing "bile acid diarrhea." The effect of bile acids on the colon has been studied; infusion of deoxycholic or chenodeoxycholic acid causes secretion of water and electrolytes into the lumen of the perfused colon. At concentrations too low to cause secretion, bile acids block colonic sodium and water absorption.[32]
4. Fatty acids are also irritating to the colon. Fatty acids are normally absorbed in the micellar form. In the absence of bile salts they enter the colon and act as irritants, causing "fatty acid diarrhea." Calcium carbonate precipitates fatty acids; therefore its oral administration may reduce the diarrhea associated with massive small bowel resection or bypass.[40]
5. Disaccharidase deficiency. This may play a role in the pathogenesis of diarrhea in two ways: (a) a high concentration of disaccharides exists in the small bowel lumen, causing an osmotic effect, and (b) the unabsorbed lactose is fermented by colonic bacteria and the resulting gas produced in the colon may increase colonic motility.

Late postoperative complications

Weight loss. This, of course, is the aim of the short bowel bypass procedure when performed for exogenous obesity. The loss is due to decreased absorption, which is a result of at least five factors: (1) fat malabsorption due to bile salt deficiency, (2) fatty acid diarrhea, (3) bile acid diarrhea, (4) increased motility and decreased transit time, and (5) decreased surface area for absorption.

Vitamin deficiencies. Of the water-soluble vitamins, vitamin B_{12} absorption is limited to the terminal ileum. Therefore bypass procedures may result in a B_{12} deficiency that, if untreated, may lead to pernicious anemia and peripheral neuropathy. A deficiency in the fat-soluble vitamin A may lead to rod and cone degeneration, which may cause night blindness; dry skin; and possibly thinning of hair. Vitamin D deficiency may lead to decreased calcium and magnesium absorption. If hypocalcemia develops acutely, it may cause tetany; chronic deficiency may result in osteomalacia. There is one report of a cardiac arrest due to hypocalcemia[18] after small bowel short-circuiting. In hypomagnesemia the low serum concentrations of magnesium lead to tetany, closely resembling that resulting from hypocalcemia. In addition, correction of the magnesium deficiency may be necessary in order to permit correction of hypokalemia or hypocalcemia.[30] It is not clear what the effect of vitamin E deficiency is in the human, but apparently it may lead to myopathy.[8] Vitamin K deficiency may lead to blood clotting disorders. Normally vitamin K catalyzes the synthesis of prothrombin by the liver. In the absence of vitamin K a hypoprothrombinemia occurs and blood clotting time may be greatly prolonged. The activities of several plasma thromboplastic factors are also reduced in vitamin K deficiency.

Diarrhea. The significance of diarrhea as a complication of the short bowel syndrome has already been discussed.

Metabolic acidosis. Metabolic acidosis may occur as a result of a loss of the alkaline fluids through diarrhea.

Hypokalemia, hypocalcemia, and hypomagnesemia. The deficits in potassium, calcium, and magnesium have already been discussed.

*Liver dysfunction.** A large proportion of very obese patients showed marked fatty infiltration on preoperative liver biopsies.[62] Following small bowel bypass, there may be some improvement in liver function,[36] but in the majority of patients there is a further depression that seems to be maximal during the first postoperative year. The cause of the liver dysfunction is unknown. There are several possibilities:

1. Lack of lipotropic agent (i.e., dietary deficiency); this may involve methionine, lecithin, choline, lipocaic, etc.
2. Lithocholic acid (Bacterial overgrowth in the remaining small intestine may result in increased formation of lithocholic acid. If absorbed in quantity, this may cause liver damage.)
3. Deficiency of a factor released by the small bowel following contact with food
4. Deficiency of an essential fatty acid
5. Toxic factor released by the excluded small bowel

Biliary calculi. Massive small bowel bypass causes bile salt and cholesterol malabsorption. Therefore it is likely that there is an alteration in the bile salt

*See references 17, 23, 25-27, 36, 37, 42, 43, 48, 52, 56, 66, 72, 75, and 79.

and cholesterol content of bile. Since cholesterol solubility requires adequate bile salt concentrations, a proportionately higher decrease in bile salt content than in cholesterol content would predispose to cholesterol gallstone formation. An increased incidence of cholelithiasis has been reported in patients with ileal resections.[31]

Nephrolithiasis. Calcium oxalate nephrolithiasis occurs with an increased incidence in patients with ileal resections.[57] Patients with jejunoileal bypass have decreased bile salt absorption; this is likely to lead to increased hepatic bile salt synthesis. Patients with increased bile acid synthesis rates have a high ratio of glycine-to-taurine–conjugated bile acids, suggesting an increased hepatic synthesis of the amino acid glycine.[33] The precursor of the bile acid glycine is not known, but it is probably glyoxylic acid, which is also the precursor of oxalic acid. With increased synthesis of bile acid glycine, the side reaction of oxalic acid synthesis may also be increased with resulting hyperoxaluria and the occasional precipitation of calcium oxalate stones.[74] In addition, because of the bile salt malabsorption, these patients "spill" glycine-conjugated bile salts into their colon, where, following bacterial deconjugation, the liberated glycine is converted to glyoxalate, which in turn is absorbed, oxidized in the liver to oxalic acid, and excreted in the urine to produce hyperoxaluria.[21] Apart from hyperoxaluria, decreased urine volume and an alteration in urine pH may also play roles in the increased urolithiasis associated with chronic diarrheal states.[19] The hyperoxaluria associated with distal ileal resection can be reversed by the oral administration of taurine.[1, 21] Such therapy may also be useful for patients with ileal bypass who develop hyperoxaluria and renal calculi.

Gastric acid hypersecretion. Gastric acid hypersecretion after massive small bowel resection has been documented both in humans and in experimental animals. We have shown in animal experiments that following resection or exclusion of the proximal third of the small bowel, there was a significant increase in gastric acid secretion; this, however, was not true for resection or exclusion of the middle or distal third. We suggested that on contact with food, a gastric inhibitory factor was released from the proximal third of the small bowel and that serotonin played a role in this inhibition.[65] Buchwald and Varco's data[12, 13] show no evidence for gastric hypersecretion in humans following distal small intestinal bypass of one third to one half of the entire small bowel length. Salmon and Wright[64] also found that jejunoileal bypass for morbid obesity in nine females did not produce any significant increase in gastric acid secretion.

Polyarthritis. Polyarthritis has been reported by Shagrin et al.[70] in 7 of 22 patients who underwent jejunocolostomy. Most of the articular manifestations were transient, lasting only a few months, but in two patients they were quite severe and lasted over 24 months. In one patient, because of the severe arthropathy, the bypass was revised to the normal anatomy; the patient had immediate, complete resolution of her symptoms. The same authors also reviewed nine patients with jejunoileostomy and none of these developed articular symptoms.

Peripheral neuromyopathy. Severe proximal muscle weakness with atrophy was reported in a patient 3½ years after a jejunocolostomy was performed for morbid obesity. Serum B_{12} and folate were within normal limits. One month following reanastomosis, examination demonstrated almost complete clinical improvement.[16]

Jejunal intussusception.[38, 48, 78] Jejunal intussusception is an infrequent complication of small bowel bypass. The intussusception occurs in the defunctional small bowel loop and should be prevented by fixing the closed end of the jejunum to the base of the mesentery.

Pulmonary embolism.[47] Operations for the treatment of massive obesity are sometimes complicated by pulmonary embolism. Increased serum fatty acid levels have been demonstrated in obese patients during and after operations. An observed inverse relationship between thrombus formation time and serum fatty acid levels in these patients was consistent with the thesis that the elevation of fatty acids is a factor in the pathogenesis of pulmonary embolism in these patients.

ADAPTATION OF REMAINING SMALL BOWEL

Diarrhea and malabsorption tend to improve with the passage of time in small bowel bypass patients even without treatment. Similarly, weight loss is most rapid during the first 18 months, less rapid during the next 12 months, and then, in most cases, weight loss ceases. Increased absorption of glucose, amino acids, sodium, and water has been reported in the remnant of intestine after massive small bowel resection.[2, 20, 84] There are at least four factors that may play a role in the adaptation of the remaining small bowel for increased absorption: (1) increase in small bowel lumen diameter and length, (2) increase in villus size, (3) changes in enzyme content (i.e., increased absorptive capacity per individual cell), and (4) induction of new functions in the remnant.

TREATMENT

The principles of management may be summarized as follows:

Phase I	Maintenance of water, acid/base, and electrolyte balance
	Antidiarrheal agents (Lomotil, codeine, and calcium carbonate)
	Low-fat (40 Gm/day) diet
Phase II	High-protein, low-fat diet
	Calcium, magnesium, and potassium balance
	Vitamin and mineral supplements
Phase III	Same as phase II; problems of lesser degree

SUMMARY

This review indicates that the complications of small bowel bypass for the treatment of morbid exogenous obesity are significant. Long-term studies are needed to show that the mortality and morbidity of the patients subjected to bypass surgery are less than those in a matched series of patients who did not have the operation. At present, bypass surgery for massive exogenous obesity must be regarded as an investigational procedure and should only be performed by units where long-term studies on the effects of the metabolic derangements will be conducted.

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8

Drains in abdominal surgery: their use and abuse

ELMO J. CERISE

No other area of surgical technique seems more controversial than the use of drains in abdominal surgery. The major reason for the vast difference in surgeons' attitudes toward drainage of the abdomen is that the decision to drain or not to drain is usually based on habit, insecurity, or emotional ideas rather than a sound scientific basis. Although the pendulum appears to be swinging in the opposite direction, a large number of surgeons uphold the dictum advocated by Tait[50] in 1887 that "when in doubt, drain." Needless to say, this attitude, which is in itself based on uncertainty, does more to cloud the issue than elucidate it.

Fortunately more and more experimental and clinical data are now appearing that can be used in the formulation of a meaningful judgment regarding abdominal drainage. But despite this there is still considerable controversy in such basics as the types of drains used, the duration of time drains are to be allowed to remain in place, and the wisdom of prophylactic drainage. The purpose of this chapter is to present an overall view of the more recent work that has been applied to this area and to propose some guidelines, based on this data, for the use or avoidance of abdominal drainage.

HISTORICAL BACKGROUND

For centuries surgeons have placed drains within the abdominal cavity despite the uncertainty of their beneficial effect. With the advent of transperitoneal operations, a great deal of importance was placed on the collections of serosanguineous fluid in the abdomen postoperatively, and the use of drains and drainage rapidly became one of the most important topics in the surgical literature during this period.[27] Reports advocating the use of tubes (most often glass, bone, or silver), rubber wicks, gauze packs, or a combination of these appeared in profusion.[58]

Hippocrates[28] first recorded the use of drainage tubes in the treatment of

empyema, and, possibly inspired by this, Celsus[9] later used them in the treatment of ascites. A review of the history of abdominal drains[58] reveals that in 1859, Chassaignac first introduced the use of soft rubber tubes. The first cigarette drain was described by Kehrer in 1882 who used gauze within the rubber sheath to avoid adhesions and increase the area of capillary drainage. Kellog in 1895 described the forerunner of the present sump-type drain, and Keaton in 1898 first applied suction to a siphon drain.

As early as 1887 Von Ott[58] and Delbet[58] independently recognized that drainage of the general peritoneal cavity is a physical and physiologic impossibility. In 1898 Halstead[25] made the comment that "no drainage at all is better than the ignorant employment of it." He pointed out some of the dangers inherent in the use of drains in the abdominal cavity and devoted many of his energies to the development of a soft drain that could be used without the danger of perforating adjacent abdominal viscera.

The monograph by Yates[58] in 1905 is considered to be a classic on the subject of abdominal drains. Confirming the work of Von Ott and Delbet, he proved experimentally that drainage of the abdomen in generalized peritonitis is of no use. His studies showed that drains are encapsulated within 6 hr unless retarded by such factors as profuse drainage. He also concluded that drains should be made of the least irritating material, and that they should be removed as soon as possible by gradual withdrawal.

INDICATIONS FOR ABDOMINAL DRAINAGE

Therapeutic indications

There are certain pathologic conditions within the abdominal wall and peritoneal cavity in which drainage is an absolute necessity for proper therapy. These

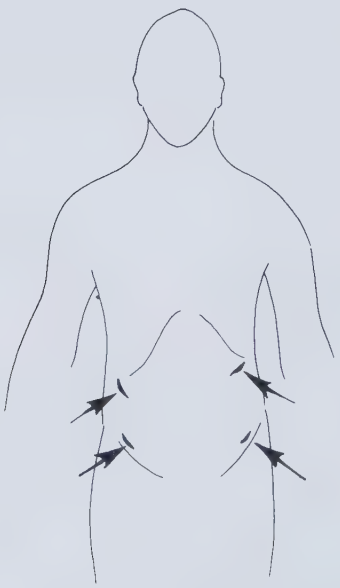

Fig. 8-1. Abdominal drain wound sites. Placed through oblique muscles and parallel to neurovascular bundles.

would include any known collection of pus, bile, or intestinal contents. The only decisions to be made in those instances are the type of drains to be used and the method of placement. The types available will be discussed in more detail and under the specific areas involved.

As a general rule, drains should be placed through a separate stab wound made parallel to the neurovascular bundles through the oblique muscles of the abdomen and sutured to the skin (Fig. 8-1). Their placement should be in the most dependent portion of the cavity to be drained. However, while desirable, this is not as important when suction is used on the drainage tube. The exit tract through the abdominal wall should be directed at the same angle through all layers. This is accomplished by placing tension on the peritoneum and fascia to bring them into normal position when the drain tract is made (Fig. 8-2). If not done, the layers of the abdominal wall will form different angles with the drain tract, resulting in kinking of the drain. There should be written documentation of the number and type of drains used and the dates of their removal.

Prophylactic indications

While there is unanimity of opinion concerning the use of drains in a therapeutic sense as discussed previously, there is no such agreement concerning their use prophylactically.

In a recent report Duthie[17] has listed the following objectives for the prophylactic use of drains within the abdomen:

1. Prevention of formation of collections of fluid—blood, pus, bile, and intestinal contents
2. Prevention of generalized peritonitis
3. Obliteration of cavities

Fig. 8-2. Method of constructing drain wound so that all layers of abdominal wall are parallel and tract is straight.

Table 8-1. Infection rate in 15,389 clean wounds*

Undrained wounds	1.5%
Closed-wound suction drains	1.8%
Penrose drain through adjacent stab wound	2.4%
Penrose drain through wound itself	4.0%

*Data from Cruse, P. J. E., and Foord, R.: Arch Surg. **107**:206, 1973.

The removal of fluid and the obliteration of cavities are readily accomplished if the drains are efficient and if placed in the correct position. However, the prevention of generalized peritonitis can only be feasible when the drain is either totally effective at a site of leakage or if it has resulted in the formation of a tract leading to the outside, allowing escape of fluid after its removal. Duthie admits that there are many conflicting opinions and evidence concerning this deceptively simple concept.

From their experimental and clinical observations, Nora et al.[38] seriously questioned whether drains should be used prophylactically because of their infectious complications. In a recent prospective analysis of 15,389 clean surgical wounds, Cruse and Foord[15] concluded that there was a significant increase in the infection rate when drains were used. The incidence of wound infections was related to both the placement and the type of drain used (Table 8-1). I also believe that prophylactic drainage may often be the source of complications and thus should be used judiciously; also, the sump suction type should be used in those infrequent instances when drains are thought to be indicated.

COMPLICATIONS OF DRAINS

The importance of possible complications associated with the placement of drains (especially prophylactic) within the abdomen cannot be overly stressed. There is increasing evidence, both experimentally and clinically, that drains are not innocuous and the dictum "when in doubt, drain" should be eschewed.

The major complications resulting from the use of drains include the following:

Retained drain
Route of infection from outside
Incisional hernia
Fistula formation
Breakdown of bowel anastomosis
Hemorrhage from drain wound
Inefficient drainage
False sense of security

Retention, all or part, of a drain within the abdominal cavity is not as unusual as it might appear. Most commonly this is a direct result of two factors: (1) failure to secure the drain to the skin by suturing or failure to tag it with a safety pin when withdrawing it over several days and (2) failure to have written documentation of the number and types of drains used and the dates of their removal. The sequelae of this—retained foreign body, infection, and possible secondary operation—can be avoided by adhering to the principles cited.

Both experimental and clinical evidence[10] have shown that there is retrograde migration of bacteria along the drain with colonization at the internal end of the

drain. The consequences of this with secondary infection and abscess formation are apparent.

Incisional hernia is most likely to occur where the stab wound is too large or where the drain is brought out through the primary incision. Frequently, in the latter, drainage spills over the wound, resulting in infection, abscess formation, evisceration, or later development of a ventral hernia.

Fistula formation is one of the more serious complications of abdominal drains. If the type of drain is too firm or if it is left in place too long, it can erode into an adjacent organ or viscus.

Drains have been shown to increase the incidence of leakage after bowel anastomosis.[3, 35] It appears that the interposition of a drain between the anastomosis and the omentum prevents small leaks from being sealed off.[3] Additionally, drains act as foreign bodies and stimulate an intense inflammatory response at the anastomotic site.[14]

An infrequent but troublesome complication of drains is hemorrhage from the drain wound. This usually occurs after the drain is advanced or pulled. In most cases a cut vessel goes unrecognized at the time that the stab wound is placed and then is effectively compressed by the drain. When the drain is removed, bleeding occurs. As previously mentioned, this can be avoided by placing the stab wound parallel to the neurovascular bundle.

Inefficient drainage can often be a problem due to either poor placement, kinking, or faulty selection of the type of drain.

Perhaps the most serious complication is that which arises when one relies on a drain as a panacea for inadequate hemostasis or technically faulty anastomosis. The prophylactic placement of a drain will not take care of these problems and only leaves the surgeon with a false sense of security, which belies good operative and postoperative management.

TYPES OF DRAINS

Technical aspects

Almost every type of material that one can imagine has been fashioned in almost every way possible in an attempt to develop the "ideal" abdominal drain. However, the most commonly used drain today, at least by American surgeons, is the Penrose drain made of latex rubber or some variation thereof. This type of soft rubber tube has many inherent disadvantages; i.e., it is irritating to tissue, easily collapsible, and has proved to allow bacterial ingress while egress of material is dependent on capillary attraction and gravity. The reasons for its popularity are that it is soft, easily sterilized, readily available, and, probably most importantly, its use has become a habit.

Suction drainage seems to have some advantages over the Penrose drain, as it does not depend on gravity and capillary attraction. It also allows accurate measurement of the material drained, eliminates skin maceration, and also eliminates large bulky dressings that must be changed frequently. This seems to have been borne out in a clinical investigation by Maitland and Mathieson.[34] It is especially true if the negative pressure from the suction is not great enough to collapse the drain or to allow adjacent tissues to occlude the inner opening. The insertion of an air vent tube (sump) averts these possible disadvantages.

Hanna[26] showed a sump placed inside a Penrose drain to be almost twice as

effective in draining a specific amount of experimentally introduced dye from the abdominal cavity of dogs than either a single rubber catheter or a Penrose drain alone. In addition to more satisfactory drainage, ingress of bacteria is less with a sump drain because the skin edges of the drainage wound closely approximate the drain. A bacterial filter incorporated into the air vent further minimizes the chances of infection.

A sump drain made of relatively soft radiopaque polyethelene and highly polished to prevent thrombin deposition is commercially available* (Fig. 8-3). Unfortunately it is produced in only one size and is not constructed with Silastic; therefore it may become occluded by a clot of necrotic debris sooner than desirable. It should be sutured in place as shown in Fig. 8-4 so that there is no restriction of airflow.

*Shirley wound drain, H. W. Anderson Products, Inc., Oyster Bay, N. Y.

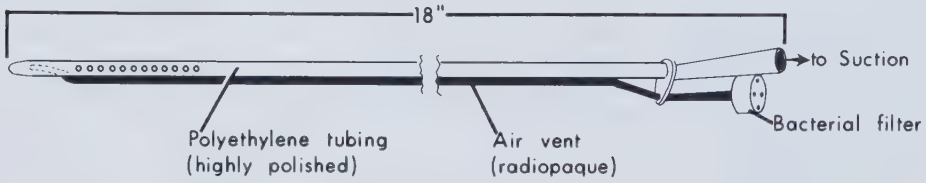

Fig. 8-3. Shirley wound drain.

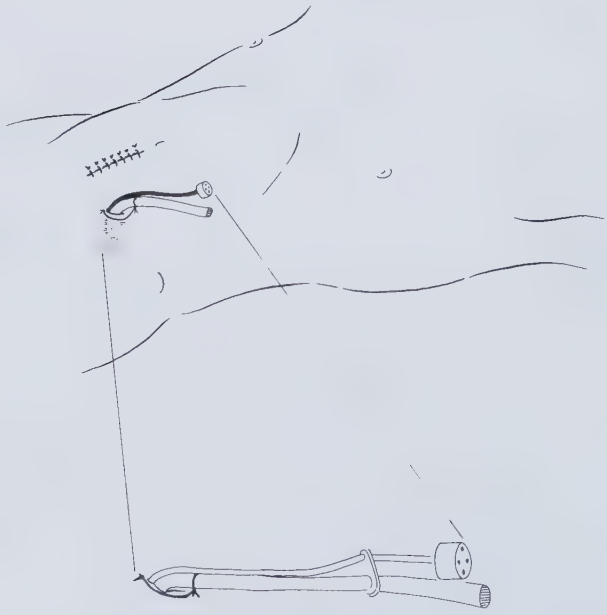

Fig. 8-4. Method of suture placement for Shirley wound drain.

Presently there are instances in which large-diameter drains are necessary within the abdomen, and the commercially available sump drains do not meet the requirements. Many surgeons have devised their own methods of obtaining sump or suction drainage by using available catheters and drains in various combinations. One such combination is illustrated in Fig. 8-5. One should always be careful in cutting additional holes in the drain so as not to make them larger than the diameter of the tube, since all drain holes distal to the largest hole would be nonfunctioning.

Despite the obvious advantages of sump drainage over the simple Penrose drains, these too are far from "ideal." The tubes presently available are for the most part rather stiff and can cause bleeding and fistula formation from pressure necrosis.

It is obvious from this discussion that at present we do not have an "ideal drain." For a drain to be ideal, it should be made of a material that is biologically and chemically inert, nonthrombogenic, soft but not easily collapsible, and readily fashioned into a variety of configurations. Additionally, a sump and bacterial filter should be incorporated into the drain. The material that presently meets most of these requirements is Silastic, a silicone polymer.* In an experimental study of

*Dow Corning Co., Midland, Mich.

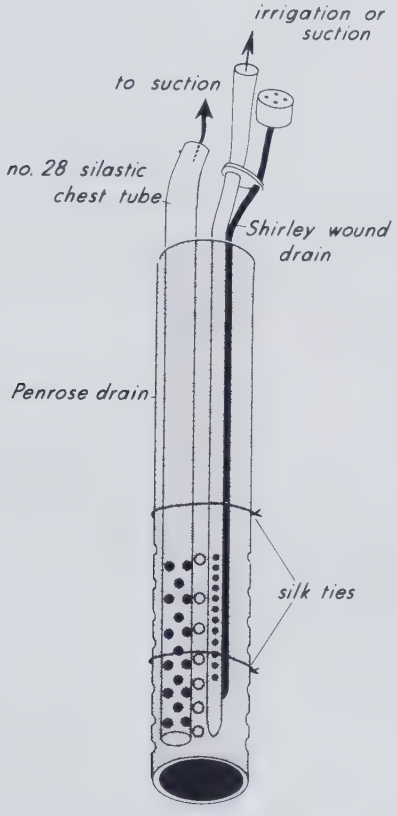

Fig. 8-5. Special large sump drain.

the reactivity of various drain materials, Crowson and Wilson[14] showed that while all types of material produced an inflammatory reaction, the most intense reactions were observed with the gauze-stuffed Penrose drain, a moderate reaction occurred to polyvinyl chloride, and a minimal response was elicited to Silastic. The only possible disadvantage to Silastic is that it is so biologically inert that it does not form a drain tract. Black et al.[4] showed that when it was placed in the abdomen of dogs, no tract was formed even after 2 months. He used T-tubes constructed of this material in seven patients with bile duct carcinoma without difficulty. While there are thoracotomy tubes commercially produced from this material, to my knowledge, there are as yet no abdominal drains made of Silastic.

SPECIFIC AREAS

Abdominal wall

Prophylactic "drainage" of the abdominal wall has frequently been advised in patients with generalized peritonitis to prevent wound abscess formation. It is even proposed in those instances where bacterial contamination is a possibility, especially in trauma.

Warren[53] points out that drainage was one of the five cardinal principles of the treatment of war wounds set forth by the great military surgeon Esmarch in 1878. A few persons then came to realize that the benefits of both drainage and primary closure could be gained by leaving the wound open for a few days and then closing it. Kocher in 1882 was one of these persons and Halsted in 1890 to 1891 followed. Despite their leadership, this significant technique, called "delayed primary closure" or "secondary closure" (depending on the amount of delay), has been many times forgotten and has had to be learned anew in every war (Gray, 1915; Bowlby, 1918; and Churchill, 1952).

Mervine et al.[37] recently reported a large series of patients in whom delayed primary closure of the abdominal wall was used when there was even the slightest possibility of bacterial contamination. This favorable experience with the use of polypropylene suture to close the fascia coincides with my own. They packed the

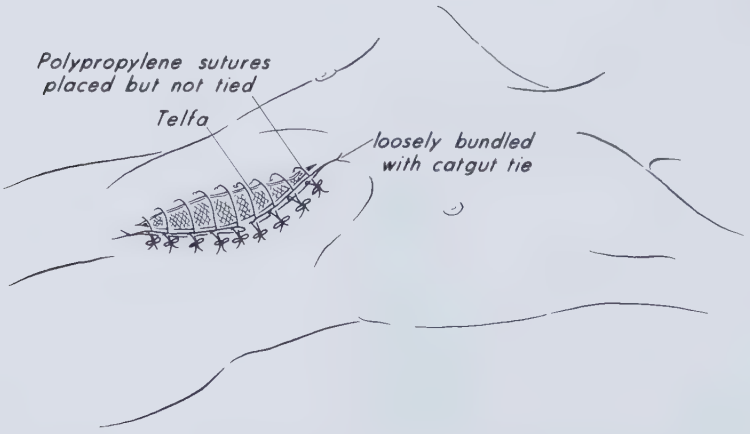

Fig. 8-6. Method of secondary wound closure in potentially contaminated wounds.

wounds open with an adherent porous gauze and closed them with paper adhesive strips in 5 to 21 days (usually 7 days). The technique I employ in this instance is to use polypropylene sutures to close the peritoneum and fascia and then place but not tie the same or similar suture material in the skin. These sutures are tied in bows and held in bundles with a catgut tie. The fat is packed with nonadherent gauze (Telfa) that is saturated with antibiotic solution (1% kanamycin or cephalothin) every 12 hr. The gauze is removed in 5 days and the sutures tied if the wound is clean. This can be done in the patient's room with only a small amount of sedation. The sutures are removed in an additional 8 to 10 days (Fig. 8-6). I do not believe that the mere placement of a Penrose drain and otherwise closing of such a wound is in any way effective in the prevention of abscess formation, and others concur in this opinion.[41]

The technique of abdominal wall closure after colectomy used by Turnbull is as follows:

1. The abdominal wall is closed with through and through interrupted wire sutures (00 or 000 usually). *Absolutely no other sutures* can be used where the skin is left open.
2. Polyethylene skin mattress sutures are placed, but not tied. They are in bundles of six and gathered together with catgut.
3. Several ½ inch strips of gauze are laid inside the incision to keep the skin edges apart.
4. The wound is wet with 1% neomycin solution every third day.
5. The gauze is removed on the ninth day.
6. Tie the polyethylene skin sutures on the 10th day.
7. Leave gaps between ties for serum to exude.
8. Remove skin sutures 10 days later.*

Following all colon resections or whenever retention sutures are used in contaminated cases, I use Telfa pledgets in the wound down to the fascia, place them between retention sutures, saturate them with antibiotics such as 1% kanamycin or cephalothin, and remove them after 8 to 9 days. The following day the wound edges between the retention sutures are taped together. This technique is illustrated in Fig. 8-7.

After repair of large ventral or umbilical hernias, there is frequently a great deal of dead space in which hematomas or seromas may collect and possibly become infected. Because of this, I use either a Shirley sump drain connected to 20 cm negative pressure or an Ethavac† drain. The latter is a portable suction apparatus available in two sizes with a device for fairly constant negative pressure of the same intensity and a calibrated collecting container. The drains are removed when drainage ceases or when they become occluded.

Following the adequate exposure of a small abdominal wall abscess, the cavity may be loosely packed with iodoform, fine-mesh gauze, nylon, or other material and changed daily or drained with a small Penrose drain. If the abscess is extensive or deep, some type of sump as described or a Silastic chest tube appropriately fashioned may be used. The fact that the drainage is adequate is much more important than the type of drain used. Drainage should be maintained until the cavity heals from its depths.

*From Turnbull, R.: Personal communication, 1973.
†Ethner Medical Products, Somerville, N. J.

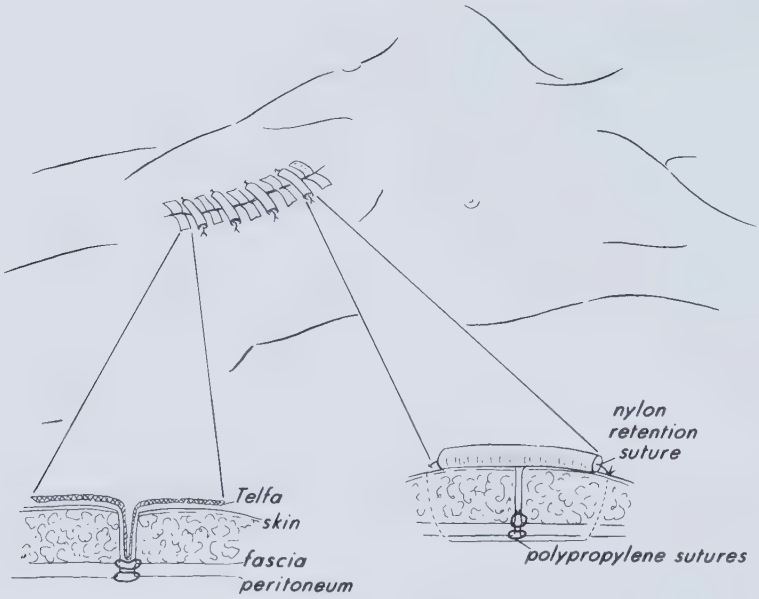

Fig. 8-7. Method of delayed primary closure used with retention sutures.

Peritoneum

Generalized peritonitis. As indicated previously, Yates[58] in 1905 proved that drainage of the peritoneal cavity was impossible, as the drains were encapsulated within 6 hr. Despite this, some authorities still recommend that in children with generalized peritonitis from appendicitis, drains should be placed in the right colic gutter and in the pelvis.[12] Other studies have shown the complications to be increased with drains in this condition, and they have concluded as I have that they are contraindicated.[32] Recently Haller et al.[24] in a randomized double-blind prospective study reported on the use of transperitoneal drainage (Penrose) in children with generalized peritonitis resulting from a ruptured appendix and found it to be ineffective. Drainage did not decrease the morbidity or mortality; consequently, they also have abandoned the use of drains.

The more pertinent question at present is the role of peritoneal lavage, peritoneal dialysis, and intraperitoneal antibiotics in the treatment of generalized peritonitis. The first reference found in the literature concerning peritoneal lavage for this condition was a paper by Price[43] of Philadelphia in 1905. He used sterile water in large amounts at the time of laparotomy. Torek[51] in 1911 is reported to have reduced the mortality in diffuse peritonitis from 100% to 40% by the use of preoperative lavage. More recently there has been both experimental evidence by Rosato et al.[47] and clinical evidence by McKenna et al.[31] to support the use of intra- and postoperative lavage or dialysis in the treatment of this condition. In a prospective study of 50 patients with generalized peritonitis, McKenna et al.[31] observed 50% fewer complications and 40% fewer deaths in the group of patients who were dialyzed with 1.5% dextrose and given systemic antibiotics as compared to the group that received systemic antibiotics only. Their technique is

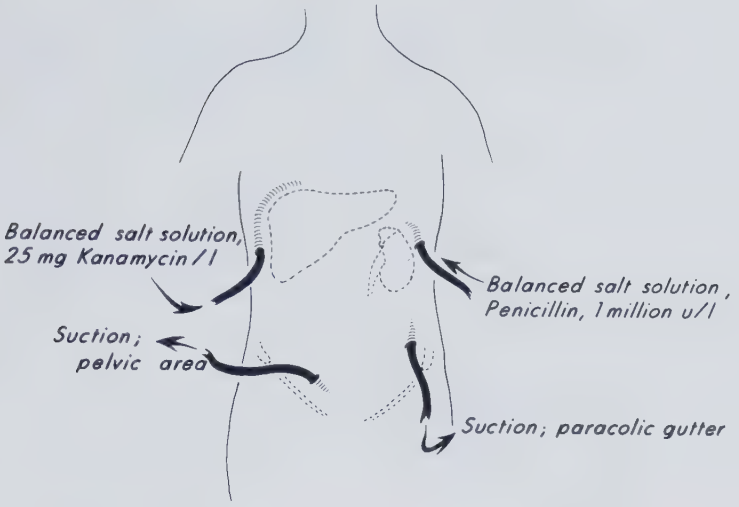

Fig. 8-8. Dialysis for acute generalized peritonitis. Technique of infusion cannulas and drain placement. Volume of fluid varies with type of inflammation and amount of debris present. In first 8 hr up to 16 L of solution are used, with kanamycin and penicillin in alternate liters. The rate is reduced to 1 L/hr and continued for 3 to 4 days. Samples of perfusate are taken at frequent intervals for examination of turbidity, electrolyte and protein content, and culture and sensitivity studies.

illustrated and described in Fig. 8-8. Currie[16] now recommends that the antibiotics be given systemically.

When one adds antibiotics to the lavage or instills them intraperitoneally by catheter placement, the evidence becomes more controversial. Rambo[44] and Altemeier[1] believe that the antibiotics are just as effective if given systemically rather than intraperitoneally provided they are given early enough, i.e., pre- or intraoperatively. However, others believe that there is an advantage to their use either in a continuous lavage[8] or instilled in the early postoperative period.[12]

Localized peritonitis or abscess formation. The conditions herein discussed are understood to be areas in which there is localized frank pus that is walled off by contiguous structures and not simply localized areas of inflammation, such as is seen with acute suppurative appendicitis or acute sigmoid diverticulitis. Intra-abdominal abscess formation may either result in spontaneous resolution, which is usual even with antibiotics, or in perforation or bacteremia. Systemic antibiotics are frequently unable to penetrate the thick wall of the abscess cavity. When an abscess extends to perforation, it follows the path of least resistance and opens into the free peritoneal cavity or an adjacent hollow viscus. The abscess wall is extremely vascular, and thus venous seeding may occur, leading to serious or fatal bacteremia. It is for these reasons that the prompt and adequate drainage of these abscesses is the sine qua non of therapy. Altemeier et al.[2] have recently provided us with an excellent description of the anatomy, incidence, bacteriology, and surgical treatment of intra-abdominal abscesses.

Generally speaking, small- to medium-sized abscesses in the subphrenic, subhepatic, appendiceal, or sigmoid areas can usually best be drained with one or more sump drains (Shirley type or similar construction). I believe that because

of their dependent position, cul-de-sac abscesses drained through the vagina or rectum can well be managed with a large Pezzer catheter (trimming the flange) or a large Foley catheter sutured to the skin and connected to a bedside container or low suction. Drainage is discontinued after several days when the patient has been afebrile and the drainage is nil.

Large abscesses, especially in the subphrenic or subhepatic spaces, frequently contain thick necrotic debris and consequently require drainage with a large tube. The extent of the abscess may require multiple incisions for adequate drainage. In this instance, I use the special type of sump drain shown in Fig. 8-5. The

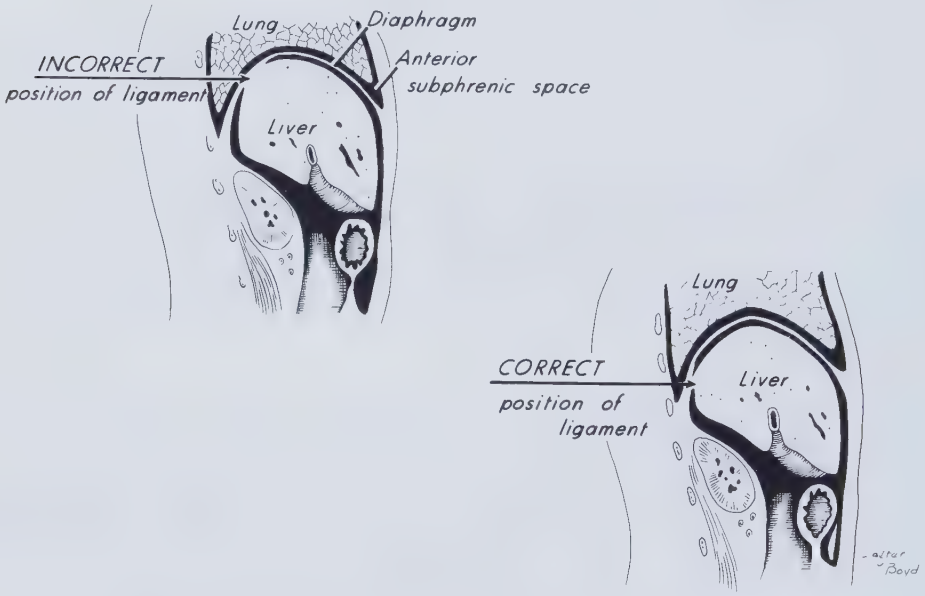

Fig. 8-9. Position of triangular ligament in relation to subphrenic spaces.

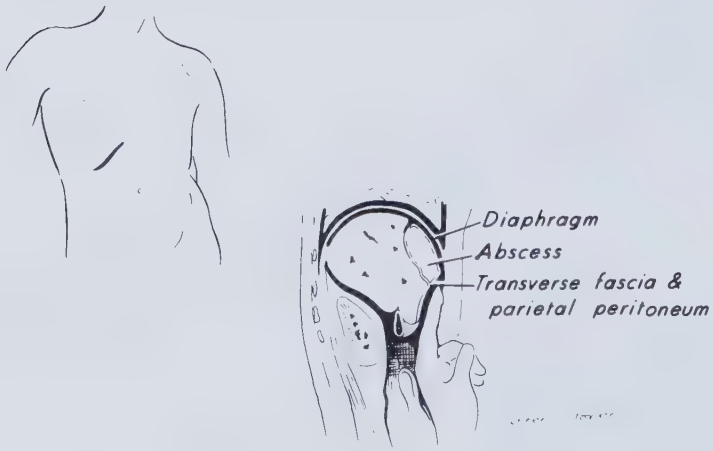

Fig. 8-10. Anterior approach to subphrenic abscesses.

anatomy of the subphrenic spaces is clearly described by Boyd,[7] who emphasizes the posterior location of the right triangular ligament (Fig. 8-9). All spaces except the right posterior subhepatic space are best drained through an anterior subcostal incision (Fig. 8-10). Halasy[23] also recommends an anterior transperitoneal approach because of the frequent multiple synchronous abdominal abscesses (22% to 29%) that would otherwise require repeat operations and have a much higher mortality. He also uses a sump drain placed in a dependent area of the abscess cavity.

Stomach and duodenum

There are few if any instances in which there is indication for peritoneal drainage after operations on the stomach. When adjacent organs are injured or resected, the indications change and these will be discussed later; however, the stomach has a rich blood supply, a thick wall, and well-formed serosa; consequently, prophylactic drainage for possible leakage is unnecessary following a technically sound operation.

The duodenum may present a problem when a difficult ulcer is encountered or when serious trauma is sustained. The study most often used to support the prophylactic drainage of the duodenal stump indicates that stump perforation is unpredictable and often fatal.[18] It was concluded that prophylactic drainage did not increase the incidence of duodenal stump leakage and provided earlier diagnosis of perforation while obviating the need for an emergency operation and lowering the mortality. However, most present-day operations for peptic ulcer will either bypass the difficult duodenum or are carefully performed so as to permit a safe anastomosis or stump closure. Rarely this is impossible and one must either perform a duodenostomy (end or side drainage) or close it insecurely and drain the area. I believe the former procedure is much safer, as it allows definitive drainage and fistula formation. Disadvantages of merely placing a drain near the closure are that it could (1) be removed before the unpredictable stump perforates, (2) contribute to leakage by being adjacent to the line of closure, and (3) be placed in or move to an area away from the site of perforation. In this unusual circumstance I prefer to use a large T-tube from the lateral wall of the closed duodenum as first described by Gingrich.[19] I clamp the tube after 10 days and only remove it after 3 to 4 weeks.

Another popular technique to accomplish internal drainage of the duodenal stump is performed by threading a Levin tube into the afferent limb of the duodenum to the stump. The tube may be placed via the transnasal or gastrostomy route and allows for adequate decompression while obviating leakage and possible fistula formation when the tube is removed.

In serious traumatic duodenal injuries, closure may usually be obtained primarily or, if necessary, by a serosal patch. I do not believe peritoneal drainage is usually indicated in either instance. Pancreaticoduodenectomy is rarely necessary for severe duodenal trauma and again, if the remaining pancreas is not traumatized, I do not believe drainage should be used routinely.

Spleen

Following splenectomy as an elective procedure or for blunt trauma with no other intra-abdominal organs injured, routine drainage is contraindicated. There

is much experimental and clinical evidence to show that the infectious complication rate is much higher when drains are used under these circumstances.[10, 13, 38, 39] If the technical procedure is such that there has been likely injury to the tail of the pancreas, a sump drain to this area may be used, but it should be removed as soon as it is evident that there has been little or no leakage of pancreatic secretions.

When splenectomy is combined with resection or injury to another organ with likely contamination, such as the colon, small intestine, pancreas, stomach, or liver, some type of drainage would usually be indicated. The types of drains used and their placement depend on the associated injury.

Pancreas

In patients with acute pancreatitis, particularly the hemorrhagic or necrotizing form, there is presently controversy concerning the role of peritoneal dialysis in treatment. Advocates of the latter contend that this method permits the effective evacuation of toxic and purulent exudate, necrotic tissue fragments, and activated pancreatic enzymes.[6, 45, 47, 59] In addition, they believe cooled solution may reduce the passage of activated pancreatic enzymes into the capillary bed of the peritoneum, thus having an anti-shock action. While the number of reported cases using this method is small, the favorable clinical results[6, 15, 20, 43, 46, 58] seem to confirm the experimental results. However, three expert surgeons in this field recently expressed the belief that there was little evidence to recommend it use.[55] Two of the currently used techniques are depicted in Figs. 8-11 and 8-12.

A serious diasadvantage to the latter method (Fig. 8-13) is that it does not allow precise placement of the catheters nor does it confirm the diagnosis by exploration.

Fig. 8-11. Suggested methods of internal drainage of insecure duodenal stump.

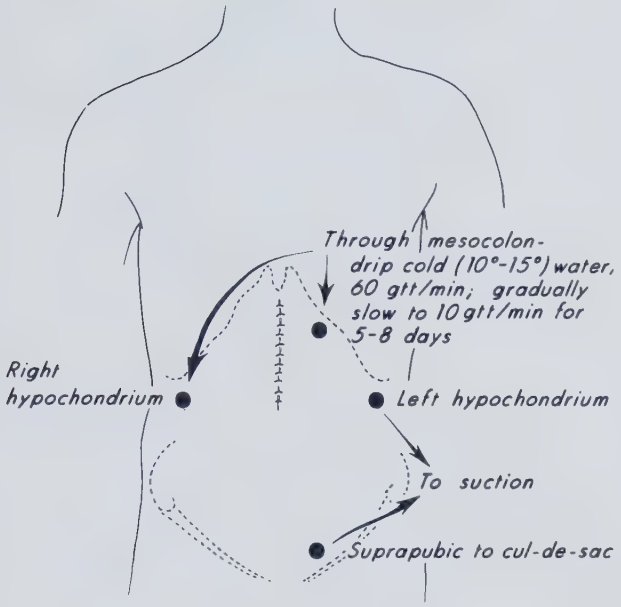

Fig. 8-12. Dialysis for hemorrhagic pancreatitis.

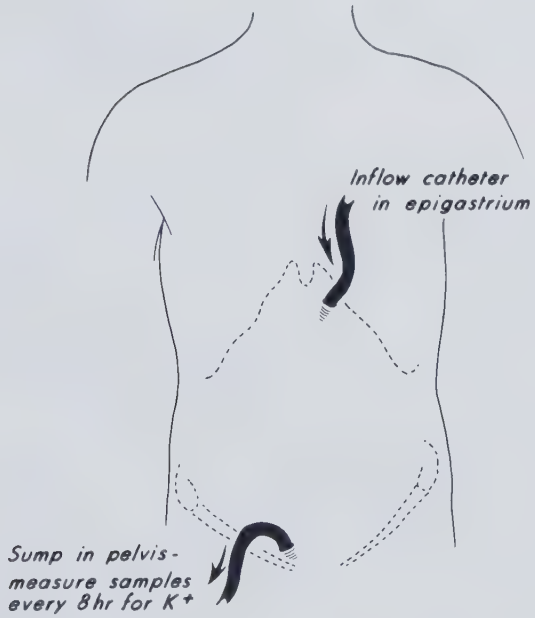

Fig. 8-13. Dialysis for acute pancreatitis. Catheter in epigastrium and sump in pelvis are inserted under local anesthesia. Instill 2 L of dialysis solution every hour for the first 8 to 16 hr, then 1 L/hr for a total of 48 to 72 hr.

Most surgeons who find hemorrhagic or necrotizing pancreatitis at operation would elect to at least drain the lesser sac if dialysis were not to be used. In this instance, I believe sump drainage using multiple drains through separate stab wounds as advocated by Zimberg[60] is much superior to the use of Penrose drains, as the serious complications of abscess formation followed by large blood vessel erosion are less likely to occur. To this procedure, others would add cholecystectomy, gastrostomy, and sometimes feeding jejunostomy.[29]

In pancreatic injuries there is often leakage of enzymatic secretions that are proteolytic and easily become loculated and infected. For this reason some type of drainage is indicated. Small lacerations of the parenchyma may be sutured and externally sump drained. However, when the major ductal system is involved or if there has been transection of the gland, some type of internal drainage such as a Roux-en-Y anastomosis of intestine should be used. This allows for free drainage of pancreatic juice into the intestinal tract and prevents an external fistula. When the distal portion is transected or seriously damaged, it should be resected. Very rarely there will be a rupture of the main pancreatic duct and extensive injury to the duodenum and distal common duct, requiring pancreaticoduodenectomy.

In summary, more serious injuries to the pancreas can be managed by some type of internal drainage accompanied by external sump drainage. The drains should be left in place as long as there is a significant volume and especially if there are enzymes in the drainage fluid or clinical and laboratory evidence of pancreatitis.

Following pancreaticoduodenectomy for malignant disease, Gilsdorf and Spanos[18] reported that the placement of drains afforded no protection against the development of peritonitis or intra-abdominal abscesses, but rather that the incidence of these complications was twice as great and the anastomotic leaks four times as great when drains were used. From this study at least it would seem that drainage would usually be contraindicated with this operation.

Liver

All significant injuries and resections of the liver parenchyma are usually followed by some bile leakage and bleeding. This coagulum of blood and bile, if not already infected by concomitant injuries, is an excellent culture medium for bacteria and must be adequately evacuated. For this reason almost all surgeons experienced in this field recommend adequate drainage to the affected liver area. I believe this can be most appropriately accomplished by the type of special sump drain previously illustrated in Fig. 8-5, placed both anteriorly and posteriorly. These drains should not be removed until all drainage ceases and x-ray evidence by dye injection reveals that there is no longer a cavity present at the drain tip.

There remains considerable controversy regarding the placement of a T-tube in the common duct following resection for liver trauma. Proponents of the procedure, including Merendino et al.,[36] report that drainage of the biliary system reduces the bile leak from the cut surface of the liver. On the other hand, Lucas and Walt[30] recently reported in a prospective randomized study that this type of drainage was accompanied by a significant increase in morbidity and mortality and consequently felt it to be contraindicated in the treatment of penetrating liver injuries. Currently I do not employ T-tube drainage of the common bile duct in liver injuries or resections.

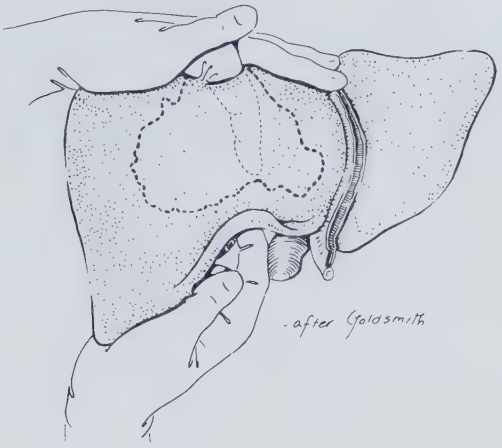

Fig. 8-14. Method of opening large intrahepatic pyogenic abscesses.

Block et al.[5] have emphasized that complications following operations for liver abscess are most frequently a result of inappropriate drainage. In an effort to prevent these complications, I believe that adequate drainage of a pyogenic abscess of the liver can best be accomplished in the manner described by Goldsmith and Chen.[21] They recommended an intraperitoneal approach through a subcostal incision, palpation, and then needle aspiration of the soft area in the liver followed by finger insertion to break down loculations and locate the most dependent portion for drainage (Fig. 8-13). My own technique is exactly as they describe except for the use of different types of drainage tubes (Fig. 8-14). The catheters are irrigated with saline solution every 8 hr until the material is returned clear and promptly, after which the irrigation catheters are removed and then the sump drain is finally removed.

In amebic abscess, specific drug therapy is always indicated and may be sufficient if the abscess is small; if larger, it may be drained percutaneously with a peritoneal dialysis catheter after adequate localization by scanning.[10] Open surgical drainage or multiple aspirations may be complicated by secondary infection.

Gallbladder and bile ducts

In a questionnaire sent to 300 members of the American College of Surgeons regarding the use of drains in various types of operations, Clemente and Maurio[11] reported that biliary surgery was one area in which there was almost unanimity of opinion that some type of drainage should be used. Of the 241 who responded, 88% used drains routinely after cholecystectomy, 95% used them after surgery for acute cholecystitis, and 93% used drains in addition to T-tube drainage when the common duct was explored. The reason given for drainage after biliary operations was to prevent the accumulation of blood and bile in the subhepatic space either due to injury to an accessory duct, improper ligation of the cystic duct, incomplete closure of the common duct, or continued ooze from the gallbladder bed.[19] I do not believe any of these indications exist in the usual technically well-performed elective cholecystectomy, and therefore I do not employ routine drainage. This opinion is supported by a recent prospective study by Williams et al.[56]

in which a Penrose or rubber tube was used in 170 patients undergoing routine elective cholecystectomy, while in 139 patients drainage was not used. They concluded that there was an increase in postoperative morbidity with drainage, especially if the drains were left for more than 48 hr. The only four patients requiring a second operation for abscess formation of bile collection were all drained "prophylactically."

When acute infection, gangrene, or localized perforation exists, drainage should be employed because the pathologic conditions make technical performance of the operation more difficult, and the conditions listed above as promoting the accumulation of blood and bile are frequently present. In addition, the presence of established bacterial infection is usually added. In these instances, routine sump drainage is usually sufficient and should be removed as soon as the clinical evidence of infection is controlled and the drainage is minimal and clear.

While there is a difference of opinion concerning the necessity of T-tube drainage following common bile duct exploration, I believe it to be helpful not for the purpose of decompressing the duct, but rather in those instances in which postoperative cholangiography is needed or when the duct is so diseased that closure is insecure. In addition to the T-tube, I employ routine sump drainage, and if there is no evidence of bile leakage, the drain is removed in 48 hr; the T-tube is removed in 8 to 10 days unless there is a specific indication for further drainage.

Intestines

There seem to be few if any indications for considering drainage in operations on the jejunum and ileum, even in cases of trauma or infection, as other technical considerations are more important for healing and the drains' mobility makes their use impractical.

Most surgeons have come to realize that drainage is not beneficial in acute appendicitis. Moreover, Magarey et al.[33] proved it to be harmful in a randomized study of 329 patients with emergency appendectomy. When drainage was employed, it was placed through the wound to the appendiceal stump, resulting in a significant increase in the number of days of fever and in the incidence of wound breakdown.

The matter of drainage as it applies to colon anastomoses seems to still be one of great controversy, especially in the difficult area of low anterior resections. Experiments have shown that drains acting as foreign bodies increase inflammatory reaction and sepsis around the anastomosis[14] and prevent sealing of small anastomotic leaks by their interposition between the suture line and the adjacent omentum or epiploicae.[3] In their studies on dogs, Manz et al.[35] showed that the inflammatory reaction was more severe and disruption of the anastomosis was much more frequent when Penrose drains were placed near the transverse colon anastomoses. The longer the drains were left in place, the worse the result.

Reviewing 454 consecutive colectomies, Berlinger et al.[3] reported a total complication rate of 24% without drains compared to 45% with drains, and anastomotic leakage of 2.5% without drains compared to 7.5% with drains. The incidence of anastomotic leak in those patients drained was even greater (23.1%) compared to those not drained (7.8%) in the series reported by Goldstein and Duff.[22] Turnbull[52] does not believe drains should be used near any colon anastomosis because of the harmful effects; however, in low colorectal anastomoses he

now places four Shirley sump drains into the presacral space and irrigates constantly for 1 week with sterile drips, using two drains in rotation for suction. He believes this prevents blood accumulation and growth of bacteria. Welch[54] is of the opinion that drains should only be used in low anterior resections because in this instance the large dead space becomes filled with blood and is easily infected. He recommends a sump drain for this situation, presumably brought out through a left lower quadrant stab wound.

In those instances in which the integrity of the low colon anastomosis is questionable, I would agree with those who advocate a proximal defunctioning colostomy.[22] To those who insist on drains, I would suggest that the drains be near "ideal," i.e., relatively nonreacting and sump, and that they be sutured so they are not directly against the anastomosis.

Following abdominoperineal resection, there has been an increasing tendency for surgeons to discontinue the use of large packs in the perineal wound princi-

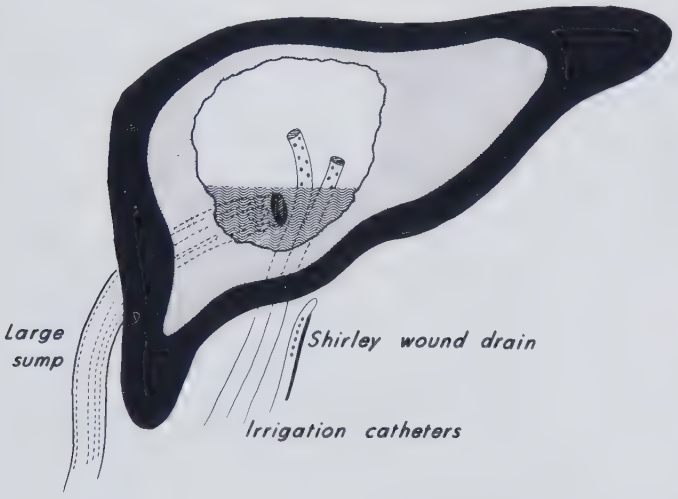

Fig. 8-15. Drainage of large intrahepatic pyogenic abscesses.

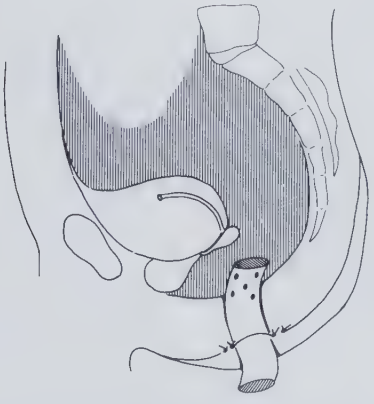

Fig. 8-16. Drainage of perineal wound following abdominoperineal resection.

pally because of the length of time necessary for healing (often 6 to 8 weeks) with the accompanying discomfort and drainage. Many have now been using primary closure, while others have inserted drains or small packs. Only in the rare instance of continued oozing from the presacral veins do I now believe that packing is necessary. My own preference is to use a short but large-bore Silastic tube sutured in place and removed when most of the drainage subsides in 5 to 6 days (Figs. 8-15 and 8-16). These wounds have very little persistent drainage and heal readily.

In severe pelvic wounds, especially if there has been significant trauma to the rectum and bladder, adequate drainage is imperative. Winegarner[57] in a report on this type of injury in Vietnam suggested that coccygectomy with wide open drainage through the presacral area is a means of establishing drainage at the time of initial debridement or later if pelvic abscesses form. He reported good results in 10 patients treated in this manner.

CONCLUSIONS AND SUMMARY

On the basis of the data reviewed in this chapter, the following guidelines for the use of abdominal drains are proposed:

1. The therapeutic use of drains to evacuate a known collection of pus, bile, or intestinal contents is indisputable.
2. Drainage for generalized peritonitis offers no reduction in morbidity and mortality and should not be employed.
3. End or side T-tube duodenostomy or internal duodenostomy are superior to simple drainage after duodenal injury or insecure closure.
4. Adequate drainage, preferably sump, is mandatory following serious liver or pancreatic trauma; however, the question of whether to use T-tube choledochostomy after hepatic resection remains unsettled.
5. The routine use of drainage following elective uncomplicated cholecystectomy does not seem to be indicated.
6. The prophylactic use of drains after uncomplicated splenectomy and colon anastomosis is contraindicated.
7. Delayed primary wound closure should be used in generalized peritonitis and should be considered in all contaminated operations, i.e., colon resections.
8. The possible complications following the use of all drains must always be carefully weighed against their potential beneficial effects.

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9

Pathophysiology, progression, and treatment of acute pancreatitis

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Acute pancreatitis is still a serious disorder and carries a mortality rate in the region of 20%. In the United States alone there were 2713 deaths from the disease in 1968, which represents an increase of 33% over the figure for 1960.[47] During the same period deaths from all causes increased by only 13%, which would suggest a true increase in the incidence of acute pancreatitis in this country. Accurate assessment of this incidence is difficult as many mild cases of the disease go undiagnosed, but if we assume that the number of deaths in 1968 represents a 20% mortality, we can estimate that there must be at least 13,000 cases of acute pancreatitis annually in the United States.

Apart from the disturbing increase in deaths from acute pancreatitis, there are several other aspects of the condition that give cause for concern. Many of the cases seen in our hospitals represent recurrent attacks of the disease, and a large percentage of these are potentially avoidable if time and effort were spent in elucidating the etiologic factors responsible for the initial episode. Hemorrhagic pancreatitis still carries a poor prognosis as reflected by recently published mortality rates of 43% to 70%,[7, 36, 48] indicating that the management of this advanced stage of the disease is still far from effective.

There are a number of reasons for this present unsatisfactory state of affairs. First, the treatment of acute pancreatitis has of necessity been empirical and supportive because not only the cause but also the mechanism of action of the various etiologic factors are unknown. Second, the nature of the early changes in human acute pancreatitis remains a mystery because it is either impossible or undesirable to biopsy the pancreas at this early stage of the disease. It is difficult to treat an

illness logically if the sequence of pathologic events is unknown. Third, it is difficult to be sure whether any therapeutic agent is of value in acute pancreatitis because of the unpredictable clinical course of the individual cases, the high rate of natural remission, and the absence of a specific test of sufficient sensitivity to monitor the progress of the disease.

In the last decade experimental and clinical research programs have been designed to provide solutions to these problems and progress has been made. This chapter will deal with some of these advances as they relate to clinical management, and new ideas on the pathogenesis and pathophysiology of the disease will be discussed.

ETIOLOGY

Although the basic cause of acute pancreatitis has not yet been identified, there is an increasing number of known conditions that predispose the patient to the development of the disease. Discovery of these etiologic factors is of considerable importance as their correction will often interrupt a recurrent pattern of the disease in the individual patient.

Approximately 40% of patients with acute pancreatitis have coexisting biliary tract pathology, including chronic cholecystitis, cholelithiasis, cholesterosis, and acalculous cholecystitis. The precise mechanism whereby these biliary abnormalities precipitate pancreatitis is unknown, although there has been no lack of hypotheses to account for the association. Reflux of normal bile into the pancreatic ductal system is now considered to be an unimportant factor in the pathogenesis of pancreatitis, since experimental and clinical studies have shown that normal bile may pass continuously along the pancreatic duct at physiologic pressures without untoward effect. Pancreatic damage may, however, be precipitated in experimental animals by abnormal constituents of bile, including β-glucuronidase and unconjugated bile acid, both of which could result from the presence of bacteria in bile. This proposed infective element in the causation of pancreatitis is supported by the findings of Lawson et al.,[45] who obtained positive bile cultures in 7 of their 15 patients with severe necrotizing pancreatitis, but it is uncertain whether such bacterial invasion is the cause or effect of the pancreatic pathology. Many workers now feel that rather than there being a causal relationship between biliary pathology and acute pancreatitis there may well be an underlying defect common to both conditions, but in the present state of our knowledge any theory as to the nature of this defect is essentially speculative.

Although alcoholism is undoubtedly linked to the occurrence of acute pancreatitis, the mechanism by which alcohol precipitates the disease is still unknown. Schapiro et al.[61] have proposed that alcohol increases pancreatic secretion by stimulating the acid-secretin mechanism and that this combined with alcohol-induced spasm of the sphincter of Oddi would elevate pancreatic intraductal pressure sufficiently to initiate the pancreatitis process. Another possibility is an alcohol-induced rise in duodenal pressure with consequent reflux of duodenal contents along the pancreatic duct, a proposal supported by the experimental studies of Rosato et al.,[59] who demonstrated that such reflux may occur at lower pressures when alcohol is present in the duodenum. On the other hand, there has been in recent years an increasing amount of evidence that alcohol may have a direct toxic effect on the pancreas. Thus long-term administration of alcohol to

rats has been reported to result in mitochondrial swelling, lipid droplet formation, and cytoplasmic degradation of pancreatic acinar cells[18] with inhibition of ^{32}P incorporation into pancreatic phospholipid.[50] The relative contribution of these factors to the pathogenesis of pancreatitis is unknown, but it would appear that any theory purporting to explain the association of alcohol and the pancreatitis process must take into consideration the high incidence of alcoholism in this country and the comparative infrequency of acute pancreatitis.

Postoperative pancreatitis may follow any abdominal operation, but it is more commonly associated with gastric surgery and operative maneuvers on the biliary tract, particularly instrumental exploration of the common bile duct. Factors incriminated in its development include direct pancreatic trauma, pancreatic duct obstruction, and vascular damage with resulting ischemia of the gland. That other mechanisms must be involved, however, is suggested by the development of acute pancreatitis after operative procedures at sites remote from the gland. A possible contributory fact in these cases could be the reduction in the level of trypsin-inhibitor concentration in pancreatic juice that has been noted to occur after surgery.

Although biliary pathology, alcoholism, and operative surgery account for the majority of cases of acute pancreatitis, there is an increasing number of other conditions that are now known to predispose the patient to an attack of the disease. In the past many of these cases would have been labeled "idiopathic," and it is hoped that with the discovery of other etiologic factors this subgrouping will eventually disappear from the pancreatitis classification.

Hypercalcelmia due to hyperparathyroidism, multiple myeloma, or hypervitaminosis D may precipitate acute pancreatitis by an as yet unknown mechanism. It has been proposed that the increased calcium concentration of pancreatic juice that accompanies hypercalcemia may produce pancreatitis by converting trypsinogen to trypsin within the gland, but the recent report of recurrent pancreatitis in a patient with normal calcium levels and a parathyroid adenoma, however, suggests that other mechanisms must be involved.[5]

That abnormal fat metabolism can occur during the course of acute pancreatitis has been recognized for many years, but only recently it has been reemphasized that hyperlipemia can be responsible for recurrent attacks of the disease. Farmer et al.[23] found that 22% of their patients with acute pancreatitis showed chylomicronemia and elevated triglyceride levels during the acute attack, and that this group of patients was particularly prone to develop recurrent attacks of pancreatitis. Investigations of these patients when their disease was in remission showed that 60% had the abnormal serum lipid patterns characteristic of familial hyperlipemia (types IV and V of Frederickson's classification). It was also noted by these workers that elevation of the plasma triglyceride level to above 1000 mg% in susceptible patients could precipitate a further attack of pancreatitis, and that restriction of the daily fat intake to below 25 Gm controlled this tendency to recurrence.

The administration of certain drugs may be associated with the development of acute pancreatitis. These drugs include chlorothiazide, isoniazid, anticoagulants, phenformin, asparaginase, and adrenal steroids. Steroid pancreatitis is important for several reasons; its incidence is increasing, it is a common cause of acute pancreatitis in children, and it carries a high mortality rate.

Other conditions that may precipitate acute pancreatitis include abdominal trauma; peptic ulceration; pancreatic duct obstruction from a variety of causes including neoplasia; infections such as viral hepatitis, mumps, and infectious mononucleosis; streptococcal food poisoning; typhoid and scarlet fevers; nutritional deficiencies such as kwashiorkor; Crohn's disease; allergy; hemochromatosis; porphyria; electric shock; Sjögren's syndrome; and, in Trinidad, scorpion stings.

PATHOPHYSIOLOGY

Although there are many factors capable of injuring the pancreas, the response of the gland to insult is rather significant in that a sequence of events is initiated that may lead to a release of activated pancreatic enzymes into and around the gland. Several natural safeguards exist within the pancreas to prevent this form of self-destruction. The normal acinar cell is peculiarly resistant to enzymatic action because of the structure of its cell membrane and the pattern of cell metabolism. Proteolytic enzymes in the acinar cell and pancreatic juice exist in the inactive zymogen form with trypsin inhibitors present not only in the pancreatic juice but also in the pancreatic substance itself. For further protection the pancreatic ductal mucosa has been shown to act as an effective barrier between activated pancreatic proteases and the gland parenchyma. Acute pancreatitis results when these natural protective devices fail.

The earliest change that occurs in the human gland is unknown, as it is rare for the pancreas to be examined at laparotomy during the first hour of the disease. Even if this were possible, it would obviously be undesirable to biopsy the gland at this stage for fear of accelerating the process. Our knowledge of these early changes must then come from studies of animals with experimental pancreatitis with all its attendant risks of misinterpretation when applied to the human disease. Bockman et al.,[9] using secretin stimulation and duct obstruction to induce pancreatitis, noted that the earliest change was the passage of normal ductal contents into the periacinar spaces between the acinar cell plasma membrane and the basal lamina. Previous studies by these investigators had shown that this fluid collection subsequently passes across the basal lamina into the interstitial area apparently by a process of passive diffusion. The presence of small amounts of enzymes in the interstitial area has been shown by Anderson et al.[1] to cause a local increase in capillary permeability and pancreatic edema, which in the presence of a higher enzyme concentration develops into frank interlobular hemorrhage. Safadi et al.,[60] studying the closed duodenal loop obstruction method to induce acute pancreatitis, also noted that the earliest change in the gland was the formation of interlobular edema and that this was followed by the appearance of focal congestion in small nonmuscular blood vessels with later extravasation of red cells within scattered acini. The bulk of the pancreatic parenchyma in this model, however, remained ostensibly normal until the late appearance of hemorrhagic zones that disrupted the lobular and acinar architecture to produce the macroscopic appearance of acute hemorrhagic pancreatitis.

This progression of acute edematous pancreatitis to the hemorrhagic form of the disease may be seen in other experimental models, and there is considerable evidence to suggest that a similar progression occurs in man. Thus the clinical onset of edematous pancreatitis may be indistinguishable from that of acute pancreatic necrosis, and patients with edematous pancreatitis at exploratory laparot-

omy may show the changes of hemorrhagic pancreatitis at later autopsy. Studies correlating the postmortem appearances of the pancreas with the duration of the illness reveal a progressive pattern of pancreatic damage ranging from minimal changes in the early deaths to total gland destruction in the late deaths.

These experimental and clinical observations indicate that acute edematous pancreatitis and acute hemorrhagic pancreatitis are but different manifestations of the same pathologic process, and that in a minority of cases there is progression from the mild to the severe form. The comparative incidence of edematous pancreatitis to hemorrhagic pancreatitis is difficult to assess, but it has been estimated that the edematous type constitutes 80% of all cases of the disease. Why the majority of patients with edematous pancreatitis do not progress to the hemorrhagic form is unexplained, but the situation raises the possibility of a naturally occurring factor that retards the progression of the pancreatitis process. There is evidence for the existence of such a retarding factor in experimental pancreatitis, acute pancreatitis associated with alcoholism, and postoperative and traumatic pancreatitis. Pfeffer et al.,[53] using a blind duodenal loop obstruction to induce experimental pancreatitis in dogs, noted that edematous pancreatitis became evident within 4 hr of the pancreatic insult. No further progression was noted during the next 6 hr until at 10 hr there was sudden onset of hemorrhagic pancreatitis associated with marked elevations in the plasma amylase levels. This 6 hr latent period has never been explained. In man when acute pancreatitis is precipitated by alcohol, pancreatic pain does not usually occur immediately after the debauch but 12 to 16 hr later, "the afternoon after the night before."[46] This delay period has never been adequately accounted for. The generally accepted explanation for the pain of alcohol-induced acute pancreatitis is an increase of pressure within the pancreatic ducts as a consequence of spasm of the sphincter of Oddi together with a secretin-mediated increase in pancreatic exocrine secretion. One would therefore expect this sequence of events to produce pain within 1 or 2 hr of alcohol ingestion unless factors preventing the progression of the pancreatitis were operating.

A latent period may also be noted in the development of acute pancreatitis due to abdominal trauma, and symptom-free intervals of up to 5 days have been reported in patients who have sustained so severe a pancreatic injury as complete transection of the gland. Similarly, in postoperative pancreatitis there is often a symptom-free interval of 24 hr between the operation and the onset of clinical manifestations of the disease. All these observations indicate that a mechanism preventing the progression of the pancreatitis may be operating and that the breakdown of such a mechanism allows the pathologic process to progress.

How might such an inhibitory mechanism operate? It has been suggested that the amount of damage in pancreatitis depends on the volume of fluid diffusing into the pancreatic tissue and the concentration of enzymes in the pancreatic juice. This suggestion is strongly supported by the work of Brown et al.,[13] who showed that the susceptibility of dogs to induced pancreatitis is directly related to the enzyme content of the pancreas at the time of insult. It has also been shown that enzymes that diffuse into the pancreatic parenchyma can cause a local vasculitis and that this may progress to thrombosis, tissue ischemia, and hemorrhagic pancreatitis.[29] After induction of experimental acute pancreatitis in animals there is a marked reduction in pancreatic exocrine secretion that is resistant to

even the strongest stimulation.[51] Furthermore, it has been shown that an increase in pancreatic exocrine secretion is a necessary factor in the production of acute pancreatitis in a traumatized gland.[51]

All these studies suggest that a decrease in the volume and enzyme content of pancreatic juice could be responsible for retarding the development of acute pancreatitis in a gland subjected to insult. The mechanism of this inhibition of pancreatic exocrine activity, however, has not been fully elucidated, although it has been proposed that glucagon release from the alpha cells of the islets of Langerhans may be contributory.[41] Glucagon has been shown to reduce the volume and enzyme concentration of pancreatic exocrine secretion,[21] and administration of the hormone to animals results in a marked degranulation of the exocrine pancreas, which is thought to result from an inhibition of enzyme synthesis.[34] Glucagon also decreases gastric secretion[55] and gastrointestinal motility,[20] effects that would inhibit secretin-mediated stimulation of pancreatic secretion. Elevated plasma glucagon levels have been reported to occur in nonfatal acute pancreatitis in dogs[51] and in man,[44] while low levels of circulating glucagon have been noted in patients with hemorrhagic pancreatitis.[41]

On the basis of these observations it has been proposed that the pancreas reacts to insult by releasing glucagon from the alpha cells and that the resulting hyperglucagonemia produced by reducing pancreatic exocrine activity would "rest" the gland for the duration of the insult. Should the insult be severe or plasma glucagon destroyed by circulating proteolytic enzymes, then the inhibitory effect of the hormone on the pancreas would be absent, thus allowing exocrine activity to resume with possible progression of the pancreatitis process.[41]

Glucagon administration to dogs with closed duodenal loop pancreatitis has been reported to increase survival time and prevent the rise in plasma amylase levels noted in untreated animals.[40] Wharton[71] demonstrated that blood in the pancreatic interlobular arteries first passes to the islet cells and then to a capillary plexus around the acinar tissue to form, in effect, a portal system between endocrine and exocrine elements of the pancreas. If glucagon release from the alpha cell is a protective device to inhibit acinar cell activity, this anatomic arrangement would be particularly well suited for its operation. Further investigation of this hypothesis is required.

Associated with the development of acute pancreatitis are biochemical, hematologic, and structural changes that, apart from being of diagnostic and prognostic value, may require correction during the course of the illness. In severe cases, up to 30% of the blood volume may be lost into and around the inflamed pancreas as a consequence of increased capillary permeability, local lymphatic obstruction, and portal hypertension. Electrolyte imbalance may result not only from the pancreatitis process but also from the effects of diminished intake, nasogastric aspiration, and renal failure, the latter being a complication of acute pancreatitis that is less rare than was previously supposed. Gjessing[28] in a recent study found that 78% of his patients with hemorrhagic pancreatitis showed evidence of renal failure with elevated serum creatinine levels and reduced urinary output despite adequate hydration therapy. With adequate supportive treatment and effective dialysis these patients with renal failure can survive, as recently demonstrated by Gordon and Calne,[30] who recorded survival in their three patients with this serious complication.

During the early stages of the acute pancreatitis process, pancreatic enzymes gain access to the bloodstream, where they may be detected by appropriate biochemical tests. Plasma amylase rises very early in the illness but falls sharply during the first 48 hr, returning to normal levels at about the fifth day. A delay in this natural resolution usually indicates continuing pancreatic damage, the presence of a pseudocyst, or occasionally renal damage. When clinical findings are equivocal and plasma amylase levels have returned to normal, standard teaching was that the more prolonged elevation in serum lipase activity could provide a useful diagnostic test of acute pancreatitis. This has recently been challenged by several workers who, using new methods of lipase determination, conclude that lipase elevations parallel those of amylase and that levels of both enzymes fall concomitantly.[12, 64] Further data are required to settle this point, perhaps in the form of a prospective study as suggested by Brooks.[12] Plasma levels of trypsin and chymotrypsin are difficult to determine in patients with acute pancreatitis because of the presence of circulating protease inhibitors and the nonspecificity of substrate used in present assay systems. The recent development of a radioimmunoassay for alpha chymotrypsin, however, may provide more reliable data, and preliminary results suggest a significant increase in plasma chymotrypsin in patients with acute pancreatitis.[25]

Plasma levels of calcium and magnesium commonly tend to fall in patients with acute pancreatitis at the end of the first week of the illness. The sequence of events leading to this hypocalcemia has not been fully elucidated, being originally attributed to the formation of calcium soaps in areas of fat necrosis. This theory, however, does not take into account the large stores of calcium in the body that are easily and rapidly mobilized should the plasma calcium level tend to fall. Furthermore, the intravenous infusion of large amounts of calcium often does not raise the plasma calcium level in acute pancreatitis, indicating that other factors must be operating. Recently Paloyan et al.[52] have suggested that elevated plasma glucagon levels in acute pancreatitis may contribute to the development of the hypocalcemia. The finding that thyroidectomy abolished hypocalcemia induced by glucagon[4] and experimental pancreatitis[62] then led to the proposal that hypocalcemic action of glucagon was mediated by thyrocalcitonin release. Glucagon infusion to a normal man, however, does not increase serum calcitonin levels,[63] and when plasma calcitonin levels are markedly elevated in patients with medullary carcinoma of the thyroid, there is no change in plasma calcium levels.[8] Furthermore, Day et al.[19] found no positive correlation between plasma calcium and glucagon levels in patients with acute pancreatitis, indicating that other mechanisms must be involved in the hypocalcemia of this condition. Condon et al.[14] have recently obtained evidence from radioimmunoassay data that the inactivation of parathormone by circulating proteolytic enzymes may be a contributory factor in its development.

Transient hyperglycemia occurs in about 50% of patients with acute pancreatitis, and diabetes is said to develop in approximately 5%.[52] The cause of this hyperglycemia is unknown, although it has been suggested that a disturbance of the normal glucagon/insulin ratio may be involved.[19] Elevated plasma levels of cortisol and growth hormone during acute pancreatitis[27] may be contributory factors, as might be the glycogenolytic effect of hyperamylasemia.

Hematologic abnormalities developing during the course of acute pancreatitis

may be useful as prognostic indices. Thus the finding of severe anemia developing during the illness indicates the presence of hemorrhagic pancreatitis, while persistence of an early leukocytosis suggests secondary infection and pancreatic abscess formation. Acute pancreatitis is often associated with an absolute lymphopenia that, although nonspecific, has certain prognostic implications in that recovery from the illness is usually accompanied by a return of the lymphocyte count to normal. Also of prognostic value is the finding of increased levels of plasma methemalbumin. In patients with hemorrhagic pancreatitis, plasma methemalbumin levels are elevated, probably as a result of pancreatic enzyme action on extravasated blood in the hemorrhagic gland; on this basis the test has been used to differentiate hemorrhagic pancreatitis from the milder edematous form of the disease. The value of this particular investigation, however, has been in question, since elevated methemalbumin levels have been recorded in nonpancreatic causes of acute abdominal pain. Allowing for this inadequacy, the test as applied in the early stages of an established case of acute pancreatitis would appear to be useful in that Kelly et al.[38] found an absolute correlation between elevated methemalbumin levels and the findings of hemorrhagic pancreatitis in animals and man.

The structural changes found in acute pancreatitis are usually consequences of local and distal effects of pancreatic enzyme activity with or without a superimposed infective element. The peritoneum reacts to the presence of irritant pancreatic enzymes with the formation of a transudate, which, if confined to the lesser sac, may lead to pseudocyst formation and, if generalized, to pancreatic ascites. Organs in the immediate vicinity of the pancreas may be affected by local enzyme action, resulting in peptic ulceration, renal symptoms, duodenal and colonic ulceration, and stenosis.

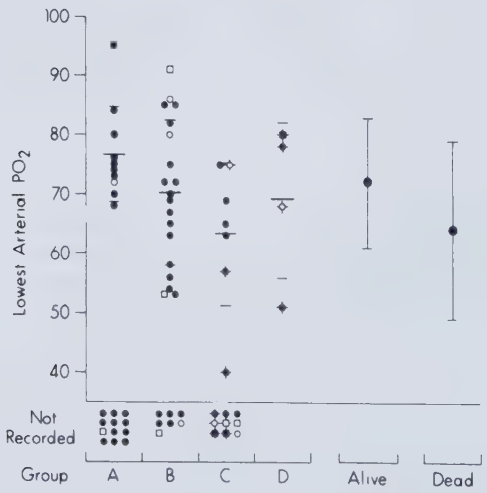

Fig. 9-1. Lowest recorded P_{aO_2} in first 48 hr in patients whose overall clinical course was: **A,** mild; **B,** moderate; **C,** severe; or **D,** catastrophic. Crossbars show mean (± SD) for each group and for those who did and did not survive. Etiology of pancreatitis is indicated as follows: ● alcoholic; ○, biliary; ■, postoperative; and □, other. + indicates death. (From Ranson, J. H. C., Roses, D. F., and Fink, S. D.: Ann. Surg. **178**:76, 1973.)

Pulmonary changes including pneumonitis, interstitial edema, atelectasis, and pneumonia are regular features of acute pancreatitis, occurring in about 20% of patients with the disease. Hypoxemia, however, is far more common and often exists without clinical or radiologic evidence of pulmonary changes. Ranson et al.[56] found that 58% of their patients with early acute pancreatitis showed arterial P_{O_2} levels below 75 mm Hg, and that there was a tendency for the degree of early hypoxemia to be related to the severity of the pancreatitis (Fig. 9-1). Pulmonary changes, when they do occur, result from a combination of diaphragmatic splinting, pleural effusions, retroperitoneal spread of pancreatic enzymes into the chest, and superimposed infection. In addition, the respiratory center may be depressed by major analgesic therapy, and there is some evidence that pulmonary surfactant may be reduced by the elevated plasma levels of phospholipase A found in acute pancreatitis. Bockman et al.[9] have recently proposed another mechanism to account for lung damage in this condition. These workers have demonstrated that certain neutrophils can ingest zymogen granules from degenerating acinar cells and reenter the circulation. The possibility has been raised that these neutrophils may become entrapped in the lung microvasculature and release these enzymes in sufficiently high concentration to cause local damaging effects.

TREATMENT

Comprehensive management of acute pancreatitis includes not only the treatment of the acute episode but the prevention of further attacks by the elucidation and correction of predisposing conditions.

Treatment of acute episode

The majority of patients with acute pancreatitis will recover in 1 week with cessation of oral intake, nasogastric suction, intravenous fluids, and analgesia. In a minority of patients, particularly those with hemorrhagic pancreatitis, the course is more severe and protracted with failure of multiple organ systems; it is this group that requires intensive effort on the part of the surgical, nursing, and laboratory staff if mortality is to be reduced. Effective management of these severely ill patients depends on the regular monitoring of vital signs together with daily biochemical and hematologic assessment using the "battery of tests" as described by Trapnell.[66] These investigations should now include hemoglobin, hematocrit, leukocyte, and lymphocyte counts and plasma urea, electrolyte, amylase, calcium, magnesium, proteins, methemalbumin, and blood gas analysis. Intelligent use of these tests will allow the clinician to detect the various complications of the disease at a time when treatment is likely to be most effective.

As the cause of acute pancreatitis is unknown, treatment is essentially supportive with correction of fluid losses, electrolyte imbalance, and hematologic and biochemical abnormalities together with adequate analgesia, control of infection, measures to reduce pancreatic exocrine activity, and surgical intervention when indicated.

The amount and nature of required intravenous fluids depends on the severity of the pancreatitis process. The patient with mild edematous pancreatitis usually requires only dextrose and saline infusions, whereas in severe hemorrhagic pancreatitis, several units of plasma and blood may be needed to maintain ade-

quate peripheral perfusion. Administration of fluids must be regulated by information obtained from clinical examination of the peripheral circulation, central venous pressure manometry, hematocrit and plasma electrolyte determinations, and hourly urine volumes. It is perhaps appropriate in this context to remind the clinician that central venous pressure manometers occasionally malfunction, and reliance on this parameter alone may lead to miscalculation of the fluid requirements.

Continuous nasogastric suction is essential in all cases. This measure reduces pancreatic exocrine secretion by inhibiting the acid-secretin mechanism, permits measurement of gastrointestinal fluid losses, and prevents vomiting that otherwise may lead to aspiration pneumonitis. We now believe that the duration of gastric aspiration should be longer than is presently practiced and probably should be continued for at least 48 hr after signs of peritoneal irritation have subsided. Anticholinergics are often employed to further reduce pancreatic exocrine activity, but as their value in the treatment of acute pancreatitis is doubtful, we do not include such agents in our treatment regimen.

Relief of pain is of considerable importance in the management of acute pancreatitis. Apart from the distress it causes the patient, severe pain accentuates the shock condition and may precipitate pulmonary complications by interfering with normal diaphragmatic function. To date no analgesic drug has been shown to be ideal for the relief of pancreatic pain. Major opiate derivatives, although probably the most effective agents, have the disadvantage of producing spasm of the sphincter of Oddi, elevation of the biliary pressure, respiratory depression, and vomiting. The benzomorphan derivatives phenazocine and pentazocine may be the analgesics of choice in this condition, as they cause less elevation in biliary pressure than morphine, and a double-blind clinical comparison of phenazocine and morphine in patients with acute abdominal pain showed no significant difference in analgesic effect.[33]

Pulmonary complications may present a considerable problem, particularly in the severe and postoperative forms of acute pancreatitis. Respiratory insufficiency must be treated early and with vigor, as there is evidence that corrective measures are far more effective at this early stage[11] and that poor peripheral oxygenation may result in further damage to an already ischemic gland. Factors contributing to respiratory insufficiency must be elucidated and corrected, using blood gas analysis to assess the effectiveness of such treatment. The dosage of analgesic agents must permit painless ventilation without depression of the respiratory center. Pulmonary edema must be controlled with diuretics, and pleural effusions causing significant impairment of lung expansion should be aspirated. Patients with atelectasis require appropriate physiotherapy and, if necessary, bronchoscopic clearance of retained secretions. Antibiotics must be used for established pneumonitis, and abdominal distention interfering with ventilation may require surgical decompression. Artificial ventilation through an endotracheal tube or tracheostomy will be necessary in some patients when other measures fail to maintain blood gases within the normal range.

The place of antibiotics in the treatment of acute pancreatitis is uncertain. Their use in the early stages does not prevent the development of the late septic complications of the disease such as pancreatic abscess, but at the same time there is no good evidence to suggest that administration of antibiotics in

this condition is harmful.[43] Nevertheless our practice is to withhold antibiotics until an indication for their administration arises on the basis that invasion by resistant organisms is less likely to occur.

Other therapeutic measures that may be required during the course of acute pancreatitis include intravenous calcium and magnesium supplements, particularly when tetany is a feature, and insulin, which may be necessary for adequate control of developing diabetes.

The introduction of the protease inhibitor aprotinin (Trasylol) over two decades ago was greeted with initial enthusiasm, but later evidence, including controlled trials on small groups of patients, suggested that its use did not materially affect the final outcome in acute pancreatitis. More recently, however, Trapnell et al.[67] in a double-blind study involving 105 patients noted a reduced mortality in patients treated with aprotinin, indicating that further evaluation of this drug is required.

In the last few years glucagon has been used in the treatment of patients with acute pancreatitis,[42] and preliminary reports of its use have been encouraging.[14, 37] Glucagon may prove to be of therapeutic value in pancreatic disease for a number of reasons. It reduces the volume and enzyme content of pancreatic exocrine secretion, and experimental studies have shown that its administration results in degranulation of pancreatic acinar cells and reduction in plasma amylase levels. Glucagon increases splanchnic blood flow, and this action may be of value in severe pancreatitis, a condition known to be associated with impaired perfusion. The hormone also reduces gastric secretion and gastrointestinal motility, and there is experimental evidence that glucagon relaxes the sphincter of Oddi.[2] Condon et al.[14] included intravenous glucagon in the treatment regimens of 50 consecutive patients with acute pancreatitis (17 classified as severe) and reported a mortality of 12%. This compares very favorably with the 20% to 23% mortality reported in other British series of patients not receiving glucagon.[22, 65, 66] Glucagon was given at a dose schedule of 1 mg as an initial intravenous injection followed by a continuous intravenous infusion of 1 mg every 4 hr in 5% dextrose solution or 0.9% saline solution for 24 to 96 hr. Noted features in treated patients included pain relief (68% required no further analgesia after glucagon) and rapid falls in plasma amylase. Plasma calcium fell minimally during treatment, and in many cases plasma calcium levels actually rose after glucagon infusion. The blood sugar, which was elevated significantly 1 hr after the initial dose of glucagon, fell thereafter to levels not significantly different from those recorded before infusion of the hormone. Glucagon therapy did not alter the incidence of the more common complications of acute pancreatitis, but no serious side effects attributable to the hormone were noted in this series. Further studies, including double-blind trials, of the use of glucagon in acute pancreatitis are being undertaken.

Peritoneal lavage as a therapeutic adjunct in the treatment of severe pancreatitis has received considerable attention since Rodgers and Carey[57] demonstrated its beneficial effects in dogs with the surgically induced disease. The concept of peritoneal lavage, however, is not a new one, but in 1937 when the procedure was advocated,[69] the mortality associated with the necessary operation was prohibitive and the practice fell into disrepute. In recent years with the development of safe peritoneal dialysis techniques, peritoneal lavage has become possible

without surgery. The rationale for this form of treatment is the fact that peritoneal fluid formed during an attack of acute pancreatitis contains substances that may be corrosive locally and toxic if absorbed into the general circulation. Those acting locally are in all probability activated pancreatic proteases, but the identification of factors causing systemic manifestations with hypotension is as yet incomplete. Vasoactive polypeptides have been demonstrated in the peritoneal fluid and bloodstream of patients with acute pancreatitis; present evidence suggests that these substances are either kinins or kinin-forming enzymes. Recent work by Hagan et al.,[32] however, suggests that an additional factor in the causation of the hypotension of acute pancreatitis may be histamine release from mast cells stimulated by pancreatic exudate. Regardless of the toxins concerned, removal of this peritoneal fluid by sump drainage[57] or peritoneal dialysis[58] results in decreased mortality rates in animals with hemorrhagic pancreatitis; there is some evidence to suggest the same may be true in man. Clinically, however, the anatomic position of the pancreas may have some bearing on the effectiveness of peritoneal dialysis, as, unlike that of the experimental animal, the human gland occupies a very deep position in the abdomen with very little contact with the general peritoneal cavity. Despite this, the early reports of the use of dialysis in clinical acute pancreatitis have been encouraging.[10, 26] Currie,[16] treating 14 patients with severe pancreatitis using this technique, noted improvement in the general condition with loss of nausea and drowsiness in all patients. Currie used an upper abdominal catheter with a large pelvic sump drain to give 2 L of peritoneal dialysis solution each hour for the first 8 to 16 hr and 1 L hourly thereafter for 2 to 3 days. Potassium losses in the effluent were corrected by the intravenous administration of potassium chloride, and antibiotics were added to the dialysis fluid when indicated. It is conceivable that the reported beneficial effects of peritoneal dialysis in acute pancreatitis may result not only from local removal of pancreatic exudate but also from the dialysis of toxic agents from the bloodstream. The finding that hemodialysis therapy did not reduce mortality in a small group of patients with severe pancreatitis and renal failure[6] does not necessarily invalidate this possibility. We do not employ peritoneal dialysis routinely in every case of acute pancreatitis, but we consider it a useful procedure in very ill patients when other measures have failed to effect an improvement. Final evaluation of peritoneal dialysis in the treatment of pancreatitis awaits properly controlled trials.

Although the majority of patients with acute pancreatitis recover uneventfully with these therapeutic measures, a certain number progress to the subacute form of the disease and develop complications that often require surgical intervention. During this protracted subacute phase, when oral intake of food is either reduced or absent, maintenance of body weight and natural resistance presents a considerable problem; in this respect the development of intravenous hyperalimentation has been a significant advance. Should sepsis contraindicate the intravenous route of administration, however, an alternative method of feeding is available in the form of an elemental diet. Such a diet contains digestible fats, amino acids, simple sugars, vitamins, and minerals and may be given through a nasogastric tube or feeding jejunostomy. Using this method in six patients with severe pancreatitis, Voitk et al.[68] noted clinical improvement, weight gain, resolution of sepsis, spontaneous closure of pancreatic fistulas, and an 80% survival

rate. Why this particular form of diet does not stimulate pancreatic exocrine activity is not clear. On the contrary, available evidence indicates that such an elemental diet depletes the gland of zymogen and actually reduces the secretion of pancreatic juice.

The role of surgery in acute pancreatitis is becoming more defined. When there is serious doubt about the diagnosis, exploratory laparotomy is indicated to exclude surgically correctable conditions such as perforated peptic ulcer, intestinal strangulation, or leaking aortic aneurysm. Contrary to previous beliefs it now appears that a properly conducted laparotomy on a well-prepared patient carries no greater risk than is associated with the patient who has not had exploratory surgery. If during such a laparotomy acute pancreatitis is confirmed, the extrahepatic biliary system should be gently palpated for calculi and the pancreas inspected through an opening into the lesser sac. If edematous pancreatitis without biliary pathology is present, the abdomen should be closed without further procedure and conservative management continued. The finding of extrahepatic biliary obstruction, however, is an indication for T-tube decompression of the common bile duct whether this obstruction is due to calculi or to compression by pancreatic edema. If nonobstructing biliary calculi are discovered at diagnostic laparotomy, the proper course of action is not absolutely defined, as there is very little published data to suggest that interference with the biliary tree during an attack of acute pancreatitis is beneficial to the patient. In the absence of such data we believe that definitive biliary surgery should be performed electively 6 weeks after resolution of the acute attack.

Scarcity of controlled data also accounts for the lack of uniformity in the surgical approach to hemorrhagic pancreatitis. Some authorities now advocate sump drainage of the peritoneal cavity and pancreatic bed to facilitate evacuation of enzyme-rich pancreatic exudate and necrotic debris.[4, 24] Waterman et al.,[70] using surgically positioned triple lumen tubes for this purpose, reported survival in 9 of their 10 patients with hemorrhagic pancreatitis, while Ziarek et al.[73] recorded only three deaths in their series of 18 patients treated with this method. A more aggressive approach has been adopted by Lawson et al.,[45] who in addition to sump drainage included cholecystostomy, gastrostomy, and jejunostomy in their treatment regimen and achieved a survival rate of 74% in a group of 15 patients with severe hemorrhagic pancreatitis. Late clinical deterioration associated with pancreatic necrosis and slough formation is being considered more and more as an indication for operation, and surgical removal of this dead tissue does appear to have a beneficial effect on the clinical course in these severely ill patients. Finally, some centers now practice total pancreatectomy for fulminating pancreatitis, but the value of this extensive procedure in these circumstances is as yet unestablished.

Surgical intervention is frequently indicated for the various complications of acute pancreatitis, including pseudocyst and pancreatic abscess, persistent obstructive jaundice, bowel stenosis or perforation, and wound dehiscence. With regard to pseudocyst formation, there is little doubt that surgery is indicated for the established encapsulated type that is enlarging or causing symptoms. The ideal treatment in these cases is some form of internal drainage such as cystogastrostomy or cystojejunostomy, depending on the site and extent of the pathology. Not so definite are the indications for operations when the only manifestation

of the pseudocyst is an asymptomatic epigastric mass, especially when this forms during the first few weeks of an attack of acute pancreatitis. Baker[4] advocates internal drainage in all cases as soon as the diagnosis is made on the basis that the pseudocyst may rupture into the peritoneal cavity or erode adjacent blood vessels, causing massive hemorrhage. On the other hand, several workers have demonstrated that pseudocysts can in fact reabsorb, and 5 of Trapnell's 18 patients[65] and 2 of Kemp's 14 patients[39] with pseudocyst showed such spontaneous resolution. On this evidence Trapnell has proposed that the existence of an epigastric mass per se is not an indication for surgery, and that drainage of a pseudocyst should only be considered if an increase in size or leakage into the peritoneal cavity occurs or if the patient's general condition shows signs of deterioration. Czaja et al.,[17] adopting such a conservative approach in 19 patients with epigastric masses developing during the course of acute pancreatitis, noted spontaneous disappearance of the swelling in eight patients before discharge from the hospital, while in 11 patients the masses persisted for longer than 3 weeks. Three of these 11 patients underwent surgery for the abdominal mass per se when the diagnosis was confirmed, while the remaining eight showed clinical and radiologic signs of spontaneous resolution of the pseudocyst during the ensuing 3 months. As precipitous rupture into the peritoneal cavity and massive hemorrhage are such rare complication of pseudocysts,[31, 49] we feel it is justifiable on the present evidence to adopt a more conservative approach to the management of pseudocysts that are not causing immediate clinical concern.

Pancreatic abscesses usually develop late in the course of acute pancreatitis and are associated with a mortality in the region of 50%. Surgical drainage should be undertaken as soon as the diagnosis has been made and antibiotic therapy instituted to deal with the septicemia that is nearly always an accompanying feature. Pancreatic abscesses are frequently multilocular due to the ease of retroperitoneal extension of the infective process, and any exploratory laparotomy for these lesions should include systematic inspection of the perinephric and pelvic areas to ensure comprehensive drainage. The insertion of tube drains into the abscess cavities will permit postoperative sinography as well as effective evacuation of the pus.

Duodenal stenosis, an uncommon complication of acute pancreatitis, is usually manifest clinically at the end of the second week of the illness and is often associated with pancreatic abscess. The condition will require gastroenterostomy if conservative management by prolonged nasogastric aspiration either fails or leads to unmanageable electrolyte difficulties.

Postoperative wound disruption is a frequent event after acute pancreatitis surgery and is potentially avoidable if special care is taken in the closure of the abdomen in such patients.

Prevention of further attacks

During the patient's hospitalization and at the follow-up clinic every effort should be made to identify the factors responsible for precipitating the initial attack of pancreatitis. Correction of these precipitating factors will often prevent recurrent episodes of the disease. Close relatives should be questioned as to the patient's alcohol consumption as he himself may deny habituation. If alcoholism is confirmed, appropriate remedial action must be taken. Investigation of the

biliary tree by cholecystography and cholangiography should be arranged approximately 1 month after the acute attack, this delay being necessary to allow any liver dysfunction to recover. Biliary pathology, if demonstrated, will require corrective surgery to prevent recurrent attacks of the pancreatitis. If peptic ulceration is suspected as an etiologic factor, barium studies with possible gastroscopy will be required before definitive treatment. Screening procedures for hyperparathyroidism and hyperlipemia may disclose the presence of further treatable conditions, and the identification of all drugs the patient may be receiving for unrelated disease may reveal one of the known agents that precipitate acute pancreatitis. Finally, a few patients with recurrent pancreatitis not responding to other measures may derive some benefit from sphincteroplasty.[35]

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10

Fat embolism: after 100 years, do we know what it is?

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Fat embolism was diagnosed as a clinical entity in 1862 when Zenker described fluid fat in the pulmonary vessels at the autopsy of a patient who died after a crushing injury. In 1873 the diagnosis was first made premortem by Von Bergmann.[218] After 100 years of clinical observations and a great mass of experimental work resulting in almost a veritable sea of ink on the subject, there are few areas in surgery that are so full of controversy, with wide disagreements in the areas of pathophysiology and treatment. The literature is profuse and confusing, a scientific Tower of Babel. Some of the confusion results from an embarrassing richness of poor papers, but much of it is due to the disease itself. There is no certain way of establishing the diagnosis before death, and all the clinical manifestations of the disease are shared with other causes that also pertain to the injured patient. Even at autopsy the disease will be missed if it is not searched for, because routine handling of tissue specimens removes the embolic fat. If searched for, it may not be found because the embolic fat resolves with time, leaving histologic changes that are completely nonspecific and that can be caused by other factors that are operative in the injured patient.

There is not a good animal model. This plus the uncertainties regarding the clinical diagnosis make evaluation of treatment very difficult indeed. A great variety of treatment regimens have had enthusiastic supporters, all citing uncontrolled clinical experience. Many of these treatments contradict each other, and some have been failures in almost every controlled trial in animals; yet a number continue to be widely used, occasionally even in the same patient.

A clear understanding of the pathophysiology of a disease is basic to intelligent management. This chapter will consider some of the more popular concepts

of the pathophysiology of posttraumatic fat embolism against a background of what is known about the clinical entity. Often lost sight of is the fact that there is a fairly sizable body of observations in this area that are reasonably well established and that must be kept in mind when evaluating past or present hypotheses concerning the nature of the disease. We will consider some of these observations as they relate to the more prominent theories of the pathophysiology of fat embolism.

We will begin with a very brief historical summary and then proceed to a consideration of specific, reasonably well-documented facts as they relate to conflicting theories of the pathophysiology of fat embolism, emphasizing data obtained from studies in patients. All areas of the syndrome cannot be covered, but many of the conflicting theories of cause and effect will be considered. A number of recent, more comprehensive reviews are available.[17, 187, 206, 218, 248]

HISTORICAL SUMMARY

Historically, fat embolism was originally considered to be a mechanical phenomenon, with fat arising from the site of mechanical injury, gaining access to disrupted veins, and becoming embolic to the lungs. There it caused problems as would any embolic material. A number of clinical observations did not easily fit this straightforward interpretation, however, and a background of misgivings concerning this mechanical interpretation burst forth in the historically very important paper of Lehman and Moore.[146] These authors overtly challenged the mechanical theory and offered an alternative—that the embolic fat arose from the circulating blood and not from any peripheral site of injury. The paper had a profound effect and seemed to change the whole tenor of subsequent studies in the field. A wide variety of alternate theories were subsequently proposed by numerous authors. Many of them began with the premise that the embolic fat arose from the circulating lipid pool and not from the site of injury.

Working in the historical context of belief in a circulating toxin as the cause of shock, Lehman and Moore[146] attempted to break the lipid suspension of dog blood with a variety of materials then associated with the shock state in injured patients. None of these in fact did break the suspension except for ether, which understandably extracted fat from the plasma phase into the ether phase. Lehman and Moore wrote a rather misleading conclusion to this long and involved section. Perhaps because of this, Scuderi in 1938[214] and again in 1941[215] misquoted their work as having established that the products of tissue decomposition and of shock can break the stability of circulating lipids. Either because of Scuderi's influential reviews or through repetition of the same error, many other authors have since similarly misstated the findings of Lehman and Moore.

The second portion of Lehman and Moore's study was a much more substantial challenge to the mechanical theory. They demonstrated that injecting most of the fat from the femoral shaft of a dog into a dog of similar size did not cause death. This quantitative challenge was subsequently refined by Armin and Grant,[9] who found that in rabbits an amount of fat sufficient to produce a histologic picture similar to what pathologists were then calling "severe fat embolism" in patients did not cause the death of the rabbits and indeed caused little apparent functional change. These observations were taken as evidence against the mechanical theory, as evidence against any pathophysiologic effects

of fat embolism, or both. This latter theme, that fat embolism is an interesting but functionally nonsignificant entity, has been supported by several authors because of the difficulty in correlating embolic fat, structural changes, and clinical symptoms.[9, 70, 91, 146, 216, 233, 234]

Partially in response to these quantitative challenges, Harris et al.[104] first suggested that fatty acids might be contributing to the pulmonary deterioration in fat embolism. The idea that fat embolism is a form of free fatty acid toxicity has taken two forms. Harman and Ragaz[103] also proposed and Peltier[185, 186, 188] in particular has developed and supported the concept of local fatty acid toxicity; i.e., embolic neutral fat is broken down locally by tissue lipase, releasing fatty acids locally in toxic concentrations. Several authors appear to equate the fat embolism syndrome in patients with the injection of free fatty acids in bolus quantities into animals, pointing out that fatty acids are extensively mobilized by the body as fuel in times of stress. The implications of this theory in terms of treatment are very important.

Among the proposals for circulating blood as the source of embolic fat, Bergentz[21] has attempted to relate fat embolism to disseminated intravascular coagulation, Clowes et al.[49] have pointed to a possible relationship to sepsis, Carlson et al.[43] have produced visceral fat deposits through excessive fat mobilization, and numerous experiments have dealt with the identification of the source of the embolic material.

In general the controversies concern two main points: the origin of the embolic fat and the mechanism of its damaging effects (if any).

EIGHT CLINICAL CLUES TO PATHOPHYSIOLOGY

Incidence of embolic fat

The incidence and degree of fat embolism are strongly related to long bone fractures, especially fractures of the femur and tibia.* Moreover, the degree of pulmonary and systemic embolization is directly proportional to the severity of the skeletal injury and is particularly high with injury to bones containing or surrounded by depot fat.†

Stainable fat is a relatively common postmortem finding if it is searched for. It can be found in a great variety of illnesses, many of which have no apparent relation to depot fat injury. This has been used by several authors as the justification for a search for a nonmechanical source for the fat.‡ Simply listing such conditions does little service to the search for facts, however, as it is very clear from series that include both posttraumatic and nontraumatic autopsy material that the fat that is found in the lungs after injury is much greater in degree and has a different distribution from what is usually described at autopsy in a variety of nontraumatic conditions.§ Even so the occurrence of intracellular or intravascular fat in these patients requires explanation. Allardyce[6] has shown that intravascular fat can form during the interval between death and autopsy in rabbits under certain conditions of premortem stress, raising a very real ques-

*See references 19, 175, 200, 206, 218, 245, and 246.
†See references 70, 93, 180, 216, 218, 237, 241, 252, and 259.
‡See references 21, 71, 124, 126, 144, 145, and 156.
§See references 70, 93, 180, 218, 237, 241, and 252.

tion of postmortem artifactual changes. Clowes et al.,[49] however, have shown that intracellular fat can develop in the lungs in dogs with peritonitis. This pattern is unlike that seen in injured patients except possibly in the late stages of resolution. Carlson et al.[13] produced intracellular fat deposits in dogs with prolonged catecholamine stimulation, but again the intracellular distribution and the pattern of involvement of the specific organs was different from what has been described in patients after injury. The Clowes and Carlson models may have much in common, and both may represent manifestations of the extensive lipid mobilization that can occur in times of stress.

Fat embolism more closely resembling the posttraumatic pattern has been found in conditions that are compatible with a mechanical origin. Fatal sickle cell crises have been associated with extensive dissemination of fat emboli.* Many of these patients also had bone marrow fragments and bone spicules in the lungs. The presumed mechanism involved acute widespread bone marrow infarction, necrosis, and swelling. Fat embolism is a common autopsy finding in dysbarism, especially caisson disease.[106-108, 110] This is easily reproducible in experimental animals[47, 52, 221] and is often accompanied by bone marrow embolization. Fatty livers are an exceptionally facile source of fat emboli and probably account for some of the posttraumatic patterns found in patients dying of nontraumatic illnesses. Alcoholics and patients with drug-induced fatty livers seem especially susceptible.[111, 127, 134, 153] Again, the pattern is easily reproduced in animals.[178] The proximity of fat globules to thin-walled veins in a soft, pulpy, incompletely protected organ seems an obvious explanation.

The incidence of fat embolism in children requires special comment. Fat embolism syndrome is rare following skeletal injury in previously healthy children. This is attributed by some to the differences between adult and juvenile marrow. The marrow in immature tubular bones is primarily hematopoietic and contains little fat. The small amount of fat that is present is composed chiefly of the glyceryl esters of stearic and palmitic acid. Olein, a fat more fluid at body temperature, predominates in mature marrow[28, 95, 214, 218] and may increase with prolonged disuse or immobilization, osteoporosis, and rickets.[95] Experimental femoral fractures in young rabbits produce a lesser degree of pulmonary fat embolism than femoral fractures in adult rabbits.[128]

Sevitt,[218] however, has found that the degree of pulmonary fat embolism in children dying of injuries correlates well with the severity of skeletal trauma. While histologic fat embolism occurs in childhood, healthy children are relatively immune to the fat embolism syndrome. We found two reports of the condition in previously healthy children with multiple femoral and tibial fractures.[2, 5] The remainder of reported cases occurred in children with predisposing conditions that altered[95] or damaged depot fat: progressive muscular dystrophy with massive fatty metamorphosis of muscle,[21] difficult manipulative reduction of fractures in obese children,[45, 132] injury to osteoporotic bones in children with congenitally dislocated hips,[63, 199] dermatomyositis,[63, 222] juvenile rheumatoid arthritis,[50, 63] and prior steroid administration and meningomyelocele.[63] The usual mechanism of bone injury was osteotomy for deformities or closed iatrogenic fracture following physical therapy or manipulation. Drummond et al.[63] reported nine

*See references 90, 176, 207, 220, and 261.

cases of fat embolism syndrome in 1800 children admitted for either pelvic or femoral fractures. Each of the nine children had one or more of the conditions mentioned. Five of these nine children died.

The syndrome seen in susceptible children parallels that in adults, but may be more rapidly fatal than the adult syndrome.[45, 63, 199, 222] However, this may also be due to bias by the authors in the selection of cases for reporting.

The incidence of fat embolism after planned injury to bone is generally low. This may be because most orthopedic procedures involve venting the damaged marrow cavity. A number of British authors have recently called attention to the high incidence of fat embolism when intramedullary prostheses are inserted through the new sealing adhesives, thus creating a piston effect in a nonvented medullary cavity.[58, 94, 177, 219]

There are rather well-documented instances when pulmonary fat embolism has occurred in humans with circulating blood as the most likely source. It is difficult to effect coalescence of oil droplets in protein systems far less stable than physiologic emulsions,[60] but destabilization of serum lipids apparently occurs under conditions of chemical[146] or mechanical abuse of blood. Fat embolism may reach 100% in autopsy material obtained after extracorporeal circulation, although it is much less in degree than that following long bone fractures.[163] Embolic fat increases linearly relative to the duration of contact between blood and gas in macrobubble oxygenators. It has been suggested that the surface tension of serum lipid particles is altered when blood and gas come in contact,[18, 179] but some of these emboli may represent tissue fat that entered the system via suction returns from the chest.

Protein molecules may be deformed at interfaces by pressure increments or decrements as small as 0.1 dyne cm^{-1}. A vacuum of 80 mm Hg in acid-citrate-dextrose bottles subjects blood to a surface force of 4782.2 dynes (gram weight) and may partially denature the lipid-stabilizing plasma proteins. Human blood collected in vacuo is destabilized to the extent that triglyceride content and lipid globules in the 2 to 10 μ range may significantly increase. Dogs autotransfused with blood collected under vacuum conditions show a greater degree of embolic fat than animals transfused with blood collected by gravity.[165] A low degree of fat embolism has been correlated with extensive transfusion of stored blood,[123, 163] but the degree of embolization was clearly less than is found in patients after major fractures and was hardly present in the transfused patients who had not undergone operation.

Primarily a pulmonary disease

The lungs are most prominently involved with embolic fat following injury. Systemic embolization is commonly found only in patients with severe pulmonary embolization.* This fact favors neither group of theories concerning the origin of the embolic fat. A generalized "deprecipitation" from the circulating blood could produce primarily pulmonary involvement because most of the blood is

*See references 70, 84, 91, 93, 157, 180, 216, 218, 237, and 241.

on its way to the lungs at any one time and because the fat is an oil at body temperature. Even injection into a peripheral artery produces primarily pulmonary embolization.[51, 148, 227] Apparently systemic pressures are sufficient to force most of the oil through, whereas the lower pressure pulmonary bed is a more efficient filter. Theories favoring local resynthesis from circulating precursors (i.e., the fat is not embolic) do have some difficulty in explaining this predominantly pulmonary distribution.

Oxygen was used with obvious clinical benefit by a number of authors[64, 141, 200] before the first controlled experimental study showed dramatic improvement in survival rates.[103] The development in the 1960's of practical and widespread methods for measuring arterial blood gases resulted in a recognition of the severe inapparent hypoxemia that commonly occurs in these patients. Since the original report of Sproule et al.,[228] there have been a large number of reports confirming the essentially universal occurrence of abnormally low arterial oxygen tensions in patients with subsequently proved or clinically likely fat embolism syndrome.* Several series have related milder degrees of hypoxemia to the degree of skeletal injury in patients without the clinical syndrome,[55, 155, 242, 255] postulating a subclinical or preclinical condition to correlate with the clinically silent fat embolism found in such patients at autopsy. Not all series have confirmed this, however.[152] These observations are of great importance in considering diagnosis and treatment but at least initially are what one would expect from any embolic material in the lungs. The only pathophysiologic concepts they bear on are those that maintain that there is little or no pathophysiologic significance to fat embolism. Concepts that fat embolism is clinically insignificant have been among the least tenable anyway and now can be safely discarded.

Time-dependent clinical and pathologic changes

Fat embolism is a syndrome with a significant time-dependent variation, both clinically and pathologically. Clinically, a latent period is often described between injury and the onset of symptoms.[120, 206, 212] Symptoms may begin almost immediately after injury or develop in the ensuing several days. It is unusual for initial symptoms to appear beyond a week after injury. The literature since 1962 is quite in agreement with Sevitt's percentages for the time of onset of symptoms.† Sevitt[218] reviewed the records of 100 patients with fat embolism and found that 25% showed symptoms inside 12 hr, 60% within 24 hr, 75% before 36 hr, and 85% within 48 hr of injury. When the onset of the syndrome is extremely rapid and the course particularly fulminant, often the patient has suffered crushing injuries to the lower extremities, holding them in a state of compression and requiring long periods of time for extrication.[8, 223, 240] It also seems that patients with osteoporosis who are subjected to brisement forcé and inadvertent closed iatrogenic fracture experience a rapidly developing and often fatal syndrome.[46, 63]

The clinically described latent period has been advanced as evidence favoring a metabolic rather than a mechanical causation. To begin with, much of the

*See references 10, 15, 20, 33, 48, 56, 74, 119, 149, 151, 154, 171, 206, 228, 250, 251, and 257.
†See references 56, 63, 169, 197, 206, and 238.

latent period is more apparent than real, as the early hypoxemia in patients with fat embolism is usually clinically undetected.[56] In addition, quantitative studies utilizing posttraumatic autopsy material have determined that the degree of pulmonary embolization varies with the time from injury. Persons killed instantly in aircraft accidents with disruption of the major vessels have less pulmonary embolic fat than those surviving the accident by several seconds.[110] The degree of embolization increases further with time from the injury and reaches a maximum in patients surviving 12 to 48 hr.[70, 93, 180, 241] Clearance of embolic fat from the lungs may become evident as early as 12 hr after injury.[180] If patients survive and reembolization does not occur, the fat emboli probably clear the lungs in 7 to 10 days.[180, 218] This pattern of initially increasing embolization and subsequent clearance of pulmonary emboli with time has been duplicated experimentally in animals.[62, 227] Direct examination of the blood draining injured and noninjured limbs in patients and animals indicates that large fat globules are released into the venous drainage of injured limbs for up to 48 hr after injury, even with apparently immobilized fractures.[130, 162, 170, 184] Such studies also provide important direct evidence in support of the mechanical theory for the origin of embolic fat. The latent period can then be interpreted as a time during which continued embolization is building to a clinically apparent threshold.

The latent period must also be considered in the context of evidence favoring a late, "chemical" phase of pulmonary deterioration following embolization with neutral fat.[103, 186] Hemorrhagic changes develop in the lungs of several species within a few days of embolization with neutral fat.[54, 102, 104, 262] These changes occur at a time when stainable neutral fat is decreasing and are associated with a worsening of hypoxemia.[54] A similar pattern can be seen in human autopsy material when the time element is taken into account.[260] Fatty acids may remain in lung tissue at a time when the embolic neutral fat is disappearing,[76] but similar changes were seen with metabolically inert embolic material.[105] In view of the deleterious effects of unbound fatty acids in small concentrations on capillary integrity and the compatible time course of structural changes in embolized lungs, this aspect of a chemical theory for fat embolism remains attractive, but firm proof has not been offered.

Difficulty in correlating amount of embolic fat with structural and clinical changes

There is some correlation of structural changes with the distribution and degree of fat embolism in human lungs, but occasionally this is quite poor. Some of this is because of the many other factors that contribute to pulmonary damage in seriously injured patients.[53, 66, 166] Even when these factors are taken into consideration, marked variability in pulmonary pathology is the rule. Some authors have even concluded that there is no correlation between the observed histologic changes and the presence of embolic fat.[70, 216, 218, 245]

Most autopsy series have not considered the time element in evaluating the relationship between embolic fat and pathologic changes. Wyatt and Khoo[260] in 1950 indicated that this might be very important in human autopsy material, in that the pathologic changes that have been described appeared only in those who survived injury for hours to days and tended to increase with increasing time of survival. This, of course, does not prove a causal relationship between

the embolic fat and the pathologic changes because of the many uncontrolled variables in the clinical situation, but the few experimental studies that have included the time element support this concept of time-dependent development of pathologic changes induced by embolic neutral fat.[54, 103, 104, 246]

More pertinent are the quantitative problems already referred to. It seems quite obvious that some pathologists have been overly enthusiastic in attributing morbidity and even morality to degrees of pulmonary fat embolism that were probably clinically insignificant, but this should not obscure the fact that embolic fat can cause pulmonary insufficiency. Confusion has been compounded by experimental studies using dogs, which have proved to be extraordinarily resistant to the effects of embolic oil even when compared to other laboratory animals.* With such marked species differences, we must rely heavily on the few indirect quantitative indications in man that are available. One such category of data includes the studies of pulmonary function in man following lymphography. Lymphography is performed with iodinated poppy-seed oil, which is obviously different from depot fat and is injected into lymphatics with an unknown and variable amount reaching the lungs. Nevertheless, morbidity and mortality have been reported that closely resemble the fat embolism syndrome† with radiologic[59, 88, 173, 174] and pathologic[139, 174] evidence of oil embolization. The severe illnesses and deaths occurred in the early days of lymphography when larger doses and more rapid rates of injection were used.[140]

Pulmonary function studies following lymphangiography are pertinent. Fraimow et al.[77] reported a patient with a rapid drop from a preinjection P_{aO_2} of 93 mm Hg to a P_{aO_2} of 60 mm Hg 1 hr after intralymphatic ethiodized oil (Ethiodol). Fabel et al.[72] reported statistically significant decreases in arterial oxygen tension 4 hr after injection: -13.3 ± 3.1 mm Hg in 10 adult patients receiving 15 to 20 ml ethiodized oil, and -7.4 ± 2.7 mm Hg in 20 patients receiving 12 to 14 ml ethiodized oil. Three groups have reported decreases in carbon monoxide diffusing capacity (D_{CO}).[73, 77, 88] The greatest decrement in D_{CO} occurred 2 to 4 hr after infusion.[77] In all these patients an unknown fraction of the injected dose remained in the regional lymphatics. The embolic dose was almost certainly well below 0.5 ml/kg.

Other forms of iatrogenic oil embolization have been reported. Carr and Johnson[41] reported the case of a 34-year-old man with a gonococcal stricture and urinary retention who died in pulmonary failure and coma 4 hr after injection of 50 ml of sterile cottonseed oil into the urethra. Twenty milliliters of the oil was found in the bladder, and the brain, kidneys, and lungs contained embolic oil at autopsy. Patterson[181] described two similar cases following traumatic instrumentation of strictures. Both patients died rapidly after urethral injection of liquid petrolatum. Both demonstrated cerebral and pulmonary symptomatology. One patient with prior cerebrovascular and respiratory disease died 15 min after a 20 ml oil injection. The other patient developed tachycardia, tachypnea, and pyrexia 30 min after the same dose. Blood cultures done at this time were negative. The patient's condition then improved, as did his ability to void. The following day, 20 ml of oil was injected with little difficulty and could be heard to

*See references 13, 37, 57, 104, 185, and 248.
†See references 1, 35, 140, 173, 174, 198, and 254.

pass into the bladder. He immediately became cyanotic and dyspneic and developed left hemiplegia and hyporeflexia. His temperature rose to 102.5° F, his pulse was 42/min, and his respirations were 27/min. He died 7 hr later. At autopsy a large amount of oil was found widely distributed throughout both lungs and kidneys. None was found in the brain, although Patterson presumed that this was due to a technical failure rather than an actual absence of oil.

None of these data deal with known and measured depot fat embolization, but they do indicate that man may be much more sensitive to embolic oil than is the dog and thereby answer much of the criticism of the mechanical theory that was based on quantitative studies in dogs. From 0.34 to 1 ml of liquid fat/kg body weight has been recovered from major fracture sites in man.[61, 241]

Bone marrow emboli found only under limited circumstances

The fact that bone marrow emboli are not usually found in patients with posttraumatic fat embolism has been used as an argument against the mechanical theory of origin. There is now enough data to indicate that this objection is probably not valid. Bone marrow, consisting of both hematopoietic elements and intact adipose tissue cells may become embolic following skeletal injury. Series including aircraft accidents have an incidence of bone marrow embolization as high as 40% and 37% in deaths considered to be immediate.[160] Bone marrow emboli are rapidly cleared from the pulmonary vascular bed, in some series in a matter of hours,[25] and as a result are most frequently found in patients dying soon after injury.[25, 75, 150, 160] By 48 hr after injury, a time when fat emboli reach their peak incidence, bone marrow emboli are rarely found,[25] although they have been described in patients dying 3 or 4 days following injury[63, 212] or longer.[75]

Bone marrow emboli may be found with embolic fat in cases of posttraumatic fat embolism syndrome.[63, 85, 147, 212] As long bones have a predominantly fatty marrow, the highest incidence of bone marrow embolism has been in patients with injuries to bones containing red marrow.[23, 25, 75, 85, 196]

Marrow emboli are bland and cause no reaction at the point of their arrest.[75] They may be quite large; one described by Lindsay and Moon[150] was 370 × 950 μ and extended for a distance of 70 μ in the lumen of a pulmonary artery. They have been reported as the primary cause of death, although this is extremely unusual.[85, 196]

Intact bone marrow emboli may pass through the vascular bed of the lung[25, 196] or gain the systemic circulation through a patent foramen ovale.[85] This may result in severe cerebral embolization and even in sudden death.[85, 196] Ghatak and Zimmerman[85] described the simultaneous occurrence of a spectrum of emboli in the cerebral vessels of a patient dying with generalized osteoporosis and multiple pathologic fractures. The emboli ranged from bone marrow to intact adipose tissue cells to fat globules not enclosed by cell membranes. Their patient had cor pulmonale and a patent foramen ovale; a correlation of autopsy findings with clinical symptomatology indicated recurrent episodes of cerebral embolization.

The important point about marrow embolization is that it seems to occur mainly at the time of injury and to be cleared rapidly from the lungs. It will therefore be found primarily in those dying soon after skeletal injury. This pat-

tern, in fact, can be interpreted as favoring the mechanical theory of the origin of embolic fat.

Shock and fat embolism in same patient

That there might be a relationship between shock and fat embolism seems to be a persistent idea. Despite clinical and experimental evidence to the contrary through the years, shock is still often mentioned as causally related to fat embolism, particularly by those favoring a metabolic origin of embolic fat. The relationship between shock and fat embolism has been discussed and investigated in three different forms: fat embolism as a cause of shock, shock as a cause of fat embolism, and the interaction between the two as a cause of death.

That fat embolism could cause hypotension was abundantly demonstrated early in this century.[87, 246] Most of the studies involved the injection of very large amounts of fat (2 to 3 ml/kg body weight) into experimental animals that then exhibited arterial hypotension, central venous hypertension, tachypnea, and death within a relatively short period of time. These observations were correlated with the frequent finding of stainable fat in the pulmonary vessels in postoperative and posttraumatic deaths, resulting in some popularity for the idea that posttraumatic shock was caused by fat embolism. Porter[192] and Sutton[231] in the military setting and Bissell[29] in the civilian world all promoted this concept during World War I. Porter was troubled by the quantitative problems involved[193] and evolved the theory that shock was caused by fat embolism of the vasomotor center.[194] As knowledge of the nature of experimental and clinical shock states has progressed, these concepts have receded into proper perspective. It is likely that massive fat embolism can indeed cause hypotension, but this must be a very unusual cause of hypotension after injury and must be a relatively infrequent occurrence (except terminally) even among patients with the clinical fat embolism syndrome.

Hemorrhagic shock as a cause of fat embolism enjoys more current popularity among some proponents of a metabolic cause for the fat embolism syndrome. The experimental evidence favoring this concept is almost nil. Hemorrhagic shock alone does not cause fat embolism in experimental animals.[169, 249] Hemorrhage followed by fracture results in less, not more, embolic fat in the pulmonary vessels,[82, 86] probably due to the decrease in bone blood flow and intramedullary pressure that accompanies hemorrhage.[105, 138] Hemorrhage at the time of the intravenous injection of fat results in higher retention in the lungs and less systemic embolization,[226] probably a result of the relatively larger number of unused pulmonary vessels in the hypovolemic animal. These can be recruited for perfusion after embolization without significantly raising perfusion pressure.

The clinical evidence supporting shock as a cause of fat embolism is also very poor. As noted previously, fat embolism is a sequel of long bone fractures. It has not been a common finding in conditions that involve even greater blood loss but less depot fat injury, e.g., ruptured livers and spleens, ruptured aortic aneurysms, and massive gastrointestinal hemorrhage. Even in patients with long bone injuries, recent evaluations have not correlated the occurrence of the fat embolism syndrome with the degree of blood loss and hypotension,[16, 56, 169, 222] always understanding that the patients at risk as a group will have significant blood loss. We were impressed with quite the opposite correlation in our experience with combat casualties in Vietnam; the viciously destructive and nearly exsanguinating but

open high-energy missile and blast wounds with fractures appeared to have a much lower incidence of the fat embolism syndrome than the simpler closed femoral fractures that resulted from vehicular accidents.[56] Data on transfusion requirements and arterial lactate levels revealed far more extensive hemorrhage in those with the open wounds. The experience of Virgilio et al.[242] may be contrary. In a prospective study of 50 patients with isolated long bone fractures, those that developed clinical fat embolism had lower cardiac outputs on admission, but it is not clear if the types of injury were the same. At any rate they were not in the degree of hemorrhagic shock that is seen with other injuries not associated with fat embolism.

Perhaps the most outspoken recent proponent of a causal relationship between shock and fat embolism has been Fuchsig. His clinical data are unconvincing and do not establish the premise that with similar injuries the patient who has lost the most blood is the one most likely to develop fat embolism, nor that the patients who develop fat embolism are those with the most severe hypovolemia.[81] His experimental data are based on the accelerated disappearance of injected fat from a subcutaneous site after a mild hemorrhage and the subsequent finding of some of the labeled substance in the lungs.[36, 80] Embolic fat per se was not demonstrated in the lungs. The lipolytic effect of any stressful challenge, including hemorrhage, has been well documented. The degree of hemorrhage used in these studies (20% of blood volume) would have been enough to provide a stimulus without sharply reducing perfusion of the fat depots. Severe hemorrhage paradoxically reduces metabolic fat mobilization by reducing perfusion.[229]

The third relationship, that of fat embolism and shock interacting in a synergistic manner to cause death, has received considerably more experimental support. Gold and Löffler[87] reported that cats made hypotensive by exposure of the intestines died sooner when injected intravenously with fat. The doses were rather high, at least 1 ml/kg. Normal controls survived this dosage, but shock controls not given fat died in 5 hr anyway. The numbers of animals were too small to draw conclusions. Green and Stoner[92] reported much firmer data indicating increased lethality after the injection of rat fat or arachis oil into rats in tourniquet shock. The same effect of fat could be produced by substituting adenosine triphosphate (ATP) injections for tourniquet shock. Whiteley[252] confirmed the findings of increased lethality in tourniquet-shocked rats injected with fat. Harman and Ragaz[103] reported similar findings in rabbits, but the numbers were not statistically significant, and Moser and Wurnig[172] reported similar results in a few cats. It may be significant that all of these studies involved preparatory injuries that produced hemoconcentration and perhaps leakage of tissue thromboplastin into the circulation. The finding of Green and Stoner that a wide variety of tissue thromboplastins or thrombin could be substituted for fat in producing increased lethality in ATP-injected rats supports speculation that the clotting mechanism was involved in these results. Unfortunately neither clotting studies nor the effect of heparin has been studied in these models, although the favorable results with heparin reported by Saldeen[210] in rats injected with homogenized adipose tissue that obviously contained thromboplastins may be relevant.

The relationship between simple hemorrhage and fat embolism has been less well studied. Armin and Grant[9] found no increase in lethality in a rabbit hemorrhagic shock model when the animals were injected with rather low doses of fat

(0.15 ml/kg). Robinson and Soloway[203] reported that a 30% hemorrhage in rabbits did not alter the early pattern of hypoxemia after injection of moderate doses of fat. In work still in progress, we have found no effect of a 40% hemorrhage on blood gas changes over a 4-day period in rabbits injected with varying doses of depot fat up to the midlethal range. There has been a slightly increased mortality in the animals given the combined challenge.

In summary, there is little evidence to support a direct causal relationship between fat embolism and hemorrhage. Most experimental and clinical evidence that bears directly on this question is against such a relationship. There is some evidence, however, that fat embolism may interact with hemorrhage or extensive tissue damage to increase the chance of dying. This is easily understood when both challenges are considered as impairing the oxygen delivery system, but generalized clotting changes may also be involved. Hypovolemia deserves urgent treatment in the injured patient for very good and established reasons that have nothing to do with fat embolism. In later stages if fat embolism occurs, a maximum cardiac output is certainly a desirable therapeutic goal in patients who are severely hypoxemic from any cause. The numerous statements that continue to appear to the effect that the treatment of shock is important in preventing fat embolism cannot be supported by available data, however. Although these are therapeutically harmless misstatements, the field of fat embolism is replete with too much empty talk to allow more to stand unchallenged.

Frequency of coagulation changes and fat embolism occurring in same patient

Fat embolism has been linked with coagulation abnormalities in a number of ways. Some have proposed that fat embolism causes intravascular coagulation. Others hold that disseminated intravascular coagulation causes fat embolism. In either case, it is proposed that the coagulation changes may be the pathophysiologically important element of the fat embolism syndrome. Many believe that fat embolism and coagulation abnormalities can be coincidental, but not necessarily related. There are varying degrees of evidence favoring all opinions, but little that is truly conclusive.

There is a large body of evidence linking hyperlipemia with facilitated or accelerated coagulation, but the details of the relationship are still obscure.[158] Most of these studies have dealt with postprandial hyperlipemia or with the infusion of emulsified triglycerides and/or phospholipids. The effects of free fatty acids are better defined, as they promote platelet aggregation[118] and trigger the intrinsic clotting sequence by activating factor XII.[116] One can object, however, that fat embolism is not synonymous or equivalent with either hyperlipemia or with free fatty acid infusions.

The occurrence of thrombocytopenia in patients with fat embolism has been taken as evidence of a link between fat embolism and coagulation disorders. The platelet counts reported in patients with the fat embolism syndrome have been in a wide range, from 12,000 to 200,000/μl.* Thrombocytopenia lasting several days is the usual consequence of significant accidental or operative injury, however.†

*See references 20, 33, 119, 129, 149, 156, 182, and 189.
†See references 12, 115, 121, 191, 224, 230, and 263.

The platelet count is depressed further by extensive transfusion[164, 224, 230] and by sepsis.[115, 264] Severe thrombocytopenia and marked coagulation abnormalities are associated with major complications of several types and carry a poor prognosis.[12, 115, 224, 230] Most of the reported platelet counts in patients with fat embolism fall in the range reported for seriously injured patients without this syndrome. One nearly controlled study showed little difference in platelet counts between groups of similarly injured patients, one with and one without a clinical diagnosis of fat embolism.[20] The series reported by Virgilio et al.[242] was at variance in that the patients who developed fat embolism had distinctly lower platelet counts on admission, but some of these may have been in borderline shock as they also had lower cardiac outputs. Wilson et al.[255] reported on 107 patients with extremity fractures in whom hypoxemia was more frequent in those with thrombocytopenia, but the lowest average P_{O_2} and lowest average platelet counts occurred in the group with the most severe injuries.

The occurrence of petechiae in the fat embolism syndrome has been explained by two very different mechanisms: thrombocytopenia and embolization of the dermal vessels. As noted, the degree of thrombocytopenia found in patients with the fat embolism syndrome may not be very different from that found in similarly injured patients without the syndrome and is usually well above the level at which petechiae appear in noninjured patients with thrombocytopenia. Garner and Peltier[83] reported a greater number of provoked petechiae in patients with fractures, but the controls were apparently noninjured, preelective surgery patients, and platelet counts were not reported. These investigators reported that they could not find fat in the dermal vessels of biopsied petechiae, but several other investigators have found intravascular fat in most petechiae that were studied.[68, 204, 218] Thompson et al.[239] demonstrated the development of hemorrhagic infarcts associated with embolic fat by studying Sandison-Clark rabbit ear chambers. In all, the evidence at present greatly favors dermal embolization as the cause of the petechiae in fat embolism. Thrombocytopenia has little solid supporting evidence as the sole or main cause of the petechiae, although it may facilitate their appearance.

Studies of other aspects of the clotting mechanism in patients with fat embolism have been even less frequent.* Keith et al.[129] reported a patient with fat embolism and disseminated intravascular coagulation, but a platelet count of 200,000, a nearly normal factor V level, and failure to demonstrate fibrinolysis make the diagnosis questionable. Bradford et al.[33] have presented several more convincing patients, all of whom were seriously injured and seriously ill. We found no differences in clotting studies between four combat casualties with fat embolism and a larger group of similarly wounded casualties without the syndrome,[56] and Benoit et al.[20] reported little difference between similarly injured patients with and without the clinical diagnosis of fat embolism. Wertzberger and Peltier[251] have said that only a lower platelet count characterized their patients with fat embolism. The clinical evidence linking fat embolism and a major coagulation disorder is thus rather slim.

*See references 20, 33, 55, 129, and 189.

Experimentally the evidence is not much stronger. Soloway and Robinson[225] found no histologic evidence of fibrin deposition and no significant changes in platelet counts and clotting studies in rabbits injected intravenously with triolein. Baker et al.[13] reported similar findings in dogs. Saldeen[208] has reported thrombin in the lungs of rats injected with homogenized depot fat, but it is explicitly clear that the injected material also contained active tissue thromboplastin. This may also explain the good results obtained with heparin in this model.[210] Thompson et al.[239] noted that platelets and fibrin adhered to embolic fat in vivo when homogenized tissue was used, but not when the fat was extracted with ether. Of course, it may well be that homogenized tissue is closer to the clinical situation than chemically clean triglycerides. We noted lower P_{O_2}'s in rabbits after fracture than in animals with the same degree of fat embolism produced by injection of "clean" fat.[31] King et al.[136] have reported coagulation changes and fibrin deposition in animals injected with oleic acid, but this is not surprising in view of the known effects of fatty acids.

Several reports have shown thrombi in relation to embolic fat in human autopsy material.* The relationship is not absolute, however, and either thrombi or fat can be found without the other. Eeles and Sevitt[65] in fact found microthrombosis to be common in fatally injured patients with or without embolic fat. It is not surprising to find fibrin near embolic fat in those areas where tissue damage has occurred, but its occurrence in areas without apparent tissue damage raises the possibility that the embolic fat itself or associated tissue thromboplastin caused the thrombosis.[208, 239]

Anemia has often been mentioned as an accompaniment of the fat embolism syndrome. The only detailed study on this point is the single patient reported by Biron et al.[27] who appeared to have a transient hemolytic anemia, but who, unfortunately, was studied after receiving 5 units of blood. The types of injuries that patients with fat embolism sustain are typically those with classic third space losses of blood. Hidden blood losses, the delayed expansion of plasma volume after serious injury, and the expected loss of up to 25% of transfused red cells make the delayed anemia that appears in such patients not at all mysterious. As with specific clotting changes, the anemia that occurs in patients with fat embolism has not been shown to be specific for fat embolism rather than the associated injuries.

More thought provoking are the studies that have shown that fat "embolism" can *result* from intravascular coagulation in rabbits and dogs. Most of these studies have required induction of hyperlipemia in the animal in order to produce significant intravascular fat deposits.† Allardyce[5] has presented evidence that the intravascular fat that forms in the kidneys during endotoxin-induced Schwartzmann reactions in rabbits is formed only during the infarction process after cessation of blood flow and thus may not be unlike the postmortem phenomenon he described. This phenomenon might explain the odd case reported by Svane[232] in which bilateral renal and pulmonary artery thromboses were associated with intravascular fat globules 3 weeks after a minor injury. Moore and Lough[167] have de-

*See references 40, 65, 209, 217, and 243.
†See references 3, 7, 21, 97, and 101.

scribed fat deposits in vascular muscle after lodgment of platelet emboli in rabbits. Gruner[98] found platelet aggregates in many organs after a variety of injuries to rabbits, but extensive degrees of fat embolism only after fractures, less extensive degrees after contusion, hemorrhage, and induced hematomas, and none after tourniquet edema without necrosis or repeated venipuncture. This indicates that in his model fat embolism and platelet aggregation were coincidental at times but were probably not interdependent.

Intravascular fat has been an absent or minimal finding in patients dying of conditions prone to cause disseminated intravascular coagulation, e.g., prolonged shock and gram-negative sepsis. Martin et al.[159] specifically compared the intravascular fat at autopsy in patients we studied after combat injuries in Vietnam, a high percentage of whom sustained extensive skeletal injuries, and patients in the Shock Study Unit at Walter Reed General Hospital, most of whom had gram-negative sepsis when they died. The latter patients had a much higher incidence of documented disseminated intravascular coagulation before death but much less intravascular fat at autopsy. Intracellular fat can be found in animals and in patients dying of gram-negative sepsis,* but the pattern of distribution, the histologic appearance, and the quantity seen are different from what is described in the posttraumatic fat embolism syndrome.

The available evidence thus indicates that fat embolism may be associated with major clotting changes but can occur in their absence. It is reasonable to assume that any such presumed embolization of tissue in large amounts could initiate intravascular coagulation, especially in hypotensive patients. The reverse situation, intravascular coagulation in noninjured patients, does not appear to be associated with any major degree of "fat embolism."

Lipemia in injured patients not equivalent to fat embolism

We have already referred to the theory of local fatty acid toxicity as a cause of structural damage in lungs embolized with depot fat. There is a more general counterpart to this theory that holds that fat embolism is a form of systemic free fatty acid toxicity.

Free fatty acids (FFA) are indeed extremely toxic to the lung[113, 114] and experimentally produce hemorrhagic lesions and death in less than one tenth the lethal dosage of neutral fat.[104, 122, 185, 215] The intravenous injection of oleic acid produces an almost instantaneous syndrome, including severe respiratory distress,† a prompt arterial hypoxemia with normal or terminally elevated P_{aCO_2},[11, 13, 57, 136] decreased pulmonary compliance,[11, 13, 135, 136] diminished surfactant activity,[13, 102] intravascular fibrin deposition,[135] thrombocytopenia,[13, 135, 136] hemolysis,[11, 122, 136, 137] hemoconcentration,[136] rapid death,[11, 122, 185, 235] and hemorrhagic pulmonary edema.‡ Pulmonary hemorrhage, exudate, and disorganization of the alveolar architecture develops 30 min after oleic acid injection.[102] Essentially the lung is dissolved.[137]

FAA aggregate platelets and activate Hageman factor, although these effects are blocked by adequate albumin binding.[117, 118] Coagulopathy follows pulmonary arterial injection of oleic acid in the dog.[136] Vasoactive amines such

*See references 5, 7, 49, 97, and 101.
†See references 11, 13, 122, 137, 185, and 235.
‡See references 11, 13, 57, 104, 122, 183, and 235.

as serotonin, released by FAA-aggregated platelets, have been implicated in the pulmonary pathology,[168, 188] although no elevation in plasma or pulmonary lymph levels of norepinephrine, dopamine, serotonin, or 5-HIAA follows oleic acid injection in the dog.[14]

Plasma FFA levels may reach 3.29 mEq/L postabsorptively in men following exercise,[195] and 1 to 2 mEq/L after acute trauma, burns, and surgical stress.[26, 211] Major surgery on osseous tissue does not induce FFA elevations greater than those following comparable surgery on nonosseous tissues.[161] The FFA levels reported in patients with the fat embolism syndrome were no higher than those following other forms of stress,[15, 26, 195, 200] and the degree of elevation of FFA was probably related to the magnitude of injury and not to the presence or absence of clinical fat embolism.[155]

Lipoprotein lipase activity depends on an association of triglycerides with protein, and lipoprotein or albumin can provide this active substrate.[142, 143, 301] In in vitro test systems, if the albumin concentration is low or if binding sites are occupied by FFA or other substances, the rate and extent of hydrolysis of an added lipid substrate may be reduced.[202] Free fatty acids are not actually free but are bound to serum albumin and sometimes lipoproteins during transport.[78, 89] Albumin has three classes of FFA binding sites: two first-class or tight-binding sites, five second-class, and approximately 20 third-class sites. In normal human plasma, less than 0.01% of FFA are actually "free." Oleic acid has an extremely high affinity for first-class sites.[89] With a plasma albumin of 4 Gm%, saturation of the two tight-binding sites occurs at an FFA concentration of approximately 1.2 mEq/L.[117] Plasma albumin probably becomes saturated as an FFA acceptor at an FFA/albumin ratio of approximately 6:1.[202] Thus at FFA levels reported in fat embolism syndrome[15] and during stress,[26, 195, 211] a surplus of free binding sites probably exists.

Although they comprise only a small percent of total lipids, FFA make up the most metabolically active lipid fraction in plasma and have a very rapid turnover rate. While total lipids range from 360 to 820 mg% and FFA from 6 to 16 mg% (0.3 to 0.7 mEq/L), the latter may contribute 50% to 90% of the total energy needs of the body in the postabsorptive state. More than 25 Gm/hr of FFA may be transported through the plasma from triglyceride stores in adipose tissue. These FFA are either directly oxidized or reesterified with glycerol in various tissues.[78, 79] They form the main energy source for the body in times of stress as well as during starvation.[38] The systemic fatty acid toxicity theory is thus suspect on at least two points: animal models based on bolus injections of fatty acids are highly artifactual and probably produce conditions of unbound fatty acid concentrations that never occur clinically, and it is very difficult to believe that the primary energy source in time of stress could so easily destroy the organism.

An older set of concepts equates fat embolism with hyperlipermia, and this association still appears implicit in a number of currently proposed treatment regimens. Lipemia occurs in man[155, 161, 195, 211] and experimental animals[41, 124, 125, 246] as a nonspecific response to stress. Changes in the various lipid fractions are complex and variable, but elevation of FFA is a constant finding and has been discussed. Clinical studies including groups of patients with major soft tissue trauma, major skeletal injuries, and posttraumatic fat embolism syndrome show that plasma

triglycerides may decrease,[147] show no significant change,[26, 99] or increase.[155] The cholesterol/phospholipid ratio in serum lipoproteins, as well as their total levels, may change,[26, 147] but no adequate correlation has been shown between lipoprotein composition or serum levels and fat embolism syndrome. Plasma triglycerides in animals respond variously to stress. Total triglycerides[34] and very low density lipoproteins[124, 125] are elevated in rabbits after trauma and after 12 hr of norepinephrine infusion in dogs.[43] Rats may show no elevation in triglyceride or phospholipid levels after bilateral femoral fracture, although FFA increase significantly.[244] After similar fractures in dogs, lipoprotein patterns have been reported to be unchanged[100] or serum triglycerides to be decreased.[22]

Artificial lipokinesis can cause a massive flux of FFA from lipid depots. Reesterification in the liver produces various lipoproteins, transport forms of endogenous triglycerides. The liver glyceride pool is 10 times that of the plasma and is the almost exclusive source of plasma glycerides.[42, 213] If mobilization exceeds oxidative needs, lipid deposition occurs in various organs.[26, 41] Lipid is deposited free in the cytoplasm and not in membrane organelles.[256] Catecholamine infusion causes a rapid and massive FFA rise in man[211] and in experimental animals.[41, 42, 43, 69] Liver triglycerides in dogs may increase tenfold in 12 hr,[41] and within 24 hr the liver is grossly yellow and cuts like butter.[69] Lipid-staining material also appears in skeletal and cardiac muscle, bronchiolar epithelium, and the alveolar wall cells of the lung.[41, 43, 69] Such lipid deposition in the lung has been implicated in the pulmonary lesion of shock and hypotension, but the pattern of deposition is very different from that seen after fractures.[69] After prolonged norepinephrine infusion, surfactant production may be decreased in dogs.[69] This may be due to lipid overloading of alveolar wall cells.[256] Atelectasis may develop but is not associated with pulmonary edema or hemorrhagic pneumonitis.[41, 256]

Endotoxemia alone induces a severe lipemia in rabbits,[5, 7] dogs,[96, 97] and man.[97] Lipid deposition within the rabbit lung is primarily extravascular,[7] and glomerular lipid deposits develop after blood flow ceases.[12] Pulmonary capillaries in dogs may be congested with fine lipid droplets.[97] Endotoxins induce endothelial damage in the lung and patchy necrosis in the lipid-laden liver. Fat in hepatic veins and sinusoids is probably released from these zones of necrosis and may become embolic.[97]

These changes may be pertinent to Clowe's[49] demonstration of a histologically stainable intracellular fat in dogs with peritonitis. We have occasionally seen patients who died of peritonitis and who had intracellular fat in the lungs in a similar distribution. It was much less in degree and different in distribution from what is seen after fractures and its functional significance is not clear, but this mechanism might explain some similar cases that have been called fat embolism, probably erroneously.

Besides lesions from local deposition, it has, of course, been postulated that coalescence and desuspension of plasma lipids in hyperlipemic patients might produce fat embolism. Autopsy data on patients with diabetic acidosis[131] and other forms of hyperlipemia.[180] do not indicate a significant effect of premortem hyperlipemia on postmortem fat embolism. Experiments in animals have not been confirmatory either. Swank et al.[234] produced what they termed fat emboli in rabbits fed high-fat meals. The intravascular lipid staining material showing in their photomicrographs does not meet the criteria for emboli. Watson[247] was unable

to confirm their findings. Brody et al.[31] found that rabbits made hyperlipemic with cobaltous chloride injections showed fewer fat emboli than controls. When both groups were subjected to femoral fracture, triglycerides, FFA, and the number of emboli increased. Emboli did not increase more in the hyperlipemic than in the normolipemic animals. This work agrees with Peltier's[153] data on fat-fed rabbits and Whiteley's[252] on fat-fed rats.

Bergentz[21] presented some data indicating that fat droplets may form more easily on the plasma surface after multiple fractures in rabbits, but could not exclude a peripheral source for the droplets. In contrast to the previously cited authors, he found more fat emboli in animals subjected to fracture after infusion of a fat emulsion, but only in the first 12 hr. Measurement of triglyceride content in the lungs confirmed this, but the lungs of lipemic, nonfractured animals were not included as controls, and this could be significant.[109]

The measurement of lipase activity in circulating blood has been proposed as an aid in diagnosis.[4, 15, 182, 190] However, lipase activity rises in many operated and injured patients who do not exhibit the syndrome, and the highest levels in those with the syndrome have been reported in survivors who presumably had less severe degrees of fat embolism. Ross[205] in particular has questioned the value of serum lipase determinations, as he found no differences between a group of patients with fractures of the tibia or femur and age- and sex-matched controls undergoing soft tissue operations. Three patients who developed the typical syndrome, in fact, never showed an elevation of lipase above normal. Others have also been unable to demonstrate a diagnostic value for serum lipase measurements.[20, 30, 48, 151, 258]

Thus the relationship between fat embolism and hyperlipemia appears to be little more than the coincident but apparently unrelated occurrence of lipid mobilization in a seriously injured patient.

SOURCE AND MECHANISM OF EMBOLIZATION

There are two important aspects of pathophysiology that we have not dealt with because there is so little clinical data, but they are so central to our understanding of the fat embolism syndrome that at least summary statements must be made. The first centers on the mechanism by which tissue fat gains access to the venous circulation in significant amounts. There is no question regarding the fact that liquid, free-flowing fat is released in significant amounts at major fracture sites.[61, 241, 253] The precise mechanism of entrance into the circulation, which is a necessary assumption of the mechanical theory of origin, is still not clear. The dynamics of blood flow and especially of venous flow through the medullary cavity of such major bones as the femur are much more active and complex than most nonorthopedists have believed.[17] Several studies based on the injection of labeled material into fracture sites in animals indicates less, not more, embolization from these sites.[32, 236, 253] There are artifacts in all of these models, but they do point up the possibility that the areas above and below the fracture sites that have intact circulations may be the sites of entrance into the circulation, rather than the fracture hematoma itself.

The second point is the evidence dealing more or less directly with the identification of the site of origin of the embolic fat. LeQuire et al.[148] presented histochemical evidence indicating a composition for embolic fat closer to circulating

lipids than to depot lipids. Ellis and Watson[67] could not confirm this. Hillman and LeQuire[112] analyzed the fat in the lungs of patients who died with severe fat embolism and found it to resemble plasma lipids, but the method of extraction included the plasma lipids present in the pulmonary circulation.[248] Kerstell et al.[133] performed a similar study in dogs, excluding the plasma lipids by retrograde perfusion of the lung, and came to the conclusion that the embolic fat was almost identical to marrow fat and distinctly different from plasma triglycerides.

Older experiments with tourniquets and with direct staining of marrow fat prior to injury gave indirect evidence that the injured limb was the source of the embolic fat in animals.[28, 39, 184, 241] We have already referred to studies in patients and in animals showing circulating large fat globules to be much more frequent in the venous drainage of the injured limb.[130, 162, 170] The series of experiments recently reported by Kerstell et al.[133] demonstrated by a number of different labeling methods that pulmonary embolic fat in dogs came from the injured limb and not from the circulating fat pool. On balance, the available evidence certainly favors the injured limb as the source of the embolic fat, which fits in well with the clinical evidence associating the vast majority of clinical cases with direct physical injury to depot fat.

SUMMARY

The association of fat embolism with major fractures of long bones remains the strongest, although indirect, evidence favoring a mechanical mechanism of origin and embolization and is the most damaging evidence against a metabolic or humoral cause. Most of the other data available from patients are compatible with the mechanical theory, although details of the mechanism of entry of depot fat into the circulation at the site of injury are still obscure. Clotting changes, hemorrhagic shock, and hyperlipemia may occur to varying degrees in the same patients, but are not required for the occurrence of the fat embolism syndrome and may be largely coincidental, sharing a common cause. Some clotting changes may be more closely related, as mechanical embolization of tissue thromboplastins could well be a part of the syndrome. The embolic fat may exert an additional deleterious effect through lipolysis, releasing locally toxic concentrations of fatty acids, but this remains to be proved. Unfortunately the disease is difficult to reproduce in animals through the same circumstances that are associated with a significant incidence in man. There are a number of animal models that may be highly artifactual. Until better premortem diagnostic measures are available, the determination of the natural history of the disease in man and adequate evaluation of different treatment regimens will remain very difficult.

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11

Thromboembolic disease: methods of study and control

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Venous thrombosis is a common condition that occurs in every type of hospitalized patient—surgical, medical, and obstetric—and along with the associated chronic venous insufficiency and pulmonary embolism is a major source of morbidity and mortality. It is also seen in apparently normal, active individuals.

Clinical and postmortem studies in the past have defined large categories of patients who have an increased risk of developing thromboembolism but have failed to accurately delineate the immediate circumstances predisposing to early thrombus formation and the natural progression of the disease process. Recent refinement of angiographic techniques, the development of scanning procedures using radioactive isotope–labeled substances, and the use of noninvasive techniques for measuring alterations in venous flow patterns permit earlier and more accurate diagnosis. When applied prospectively, these methods may be used not only to identify patients who have an increased risk of developing thromboembolism but also to evaluate alterations in the course of the disease process produced by preventive and therapeutic methods.

In 1954 DeBakey[13] reviewed the medical literature regarding thromboembolism and found a 0.14% incidence of fatal pulmonary embolism following 3,077,495 operations, with a range of 0.01% to 0.87% in various collected series. This large fluctuation in the incidence of thromboembolic disease suggested a nonseasonal epidemic pattern over large geographic areas, and similar variations were found in individual hospital reviews. The incidence of fatal pulmonary embolism based on 374,844 autopsy cases was much higher than clinical findings (2.8% with a similar wide fluctuation from 0.21% to 23.1% in collected series).

The discrepancy between clinical diagnosis and proved autopsy diagnosis emphasizes our inability to diagnose venous disease clinically in its early stages. This unrecognized and untreated disease may lead to chronic venous insufficiency or fatal pulmonary embolism.

In a recent review by Feinleib[20] the monthly variation in mean deaths per day from venous disease in the United States was evaluated between 1962 and 1967. During this period he found a linear increase in deaths over the 5-year period with seasonal oscillations, peaks occurring in January and troughs in June and July. This data from vital statistics for the United States indicates approximately 72,000 deaths over the 5-year period and represents primary venous disease of all types. (It is well known that when thromboembolic disease occurs as a terminal event during another disease it may not be listed as the cause of death.) Coon and Willis[7] estimated that as many as 47,000 deaths/year from thromboembolism may occur in the United States, and as many as 850,000 persons suffer ulceration of the leg, the majority secondary to postphlebitic change, and an even greater number of persons have the postphlebitic syndrome.

DEEP VEIN THROMBOSIS

Thromboembolism is chiefly a disease of the lower extremities, since approximately 95% of pulmonary emboli arise below the bifurcation of the inferior vena cava. The classic findings of deep vein thrombosis involving the lower extremity are present in only 50% of patients with this disease. While one patient may present with ankle edema, tender indurated calf muscles, Homans' sign, and an increase in the temperature of the extremity, another patient may have no symptoms or the disease process may become manifest by pulmonary embolism, and another patient may insidiously develop chronic venous insufficiency with stasis ulcers. Thus venous disease of the lower extremities remains one of the most perplexing and treacherous disease problems facing the physician.

Pathophysiology

Thromboembolic disease may be considered a manifestation of the body's efforts to maintain hemostasis. Potential mechanisms of thrombus formation were described by Virchow more than 100 years ago, i.e. (1) vessel wall damage, (2) stasis of blood in the involved area, and (3) a hypercoagulable state of the blood. The initial phases of thrombus formation may be independent of plasma coagulation but dependent on platelet function and factors other than those of the clotting mechanism (Fig. 11-1). Platelets adhere to any point of endothelial damage within the vascular tree. The stimulus that precipitates platelet adherence to exposed basement membrane or subendothelial collagen fibers is not well understood. Once the platelet is adherent to the vessel wall it releases a number of substances, including epinephrine, histamine, serotonin, platelet factors 3 and 4, and adenosine diphosphate (ADP). Changes secondary to this reaction cause other platelets to adhere, forming a reversible platelet aggregation. This causes a local generation of thrombin with acceleration of the clotting mechanism. Fibrin is then deposited on the initial platelet mass, and a second release reaction occurs in which the platelets lose their granularity and become indistinguishable. This causes an inflammatory response in the vascular wall. Stasis of local blood

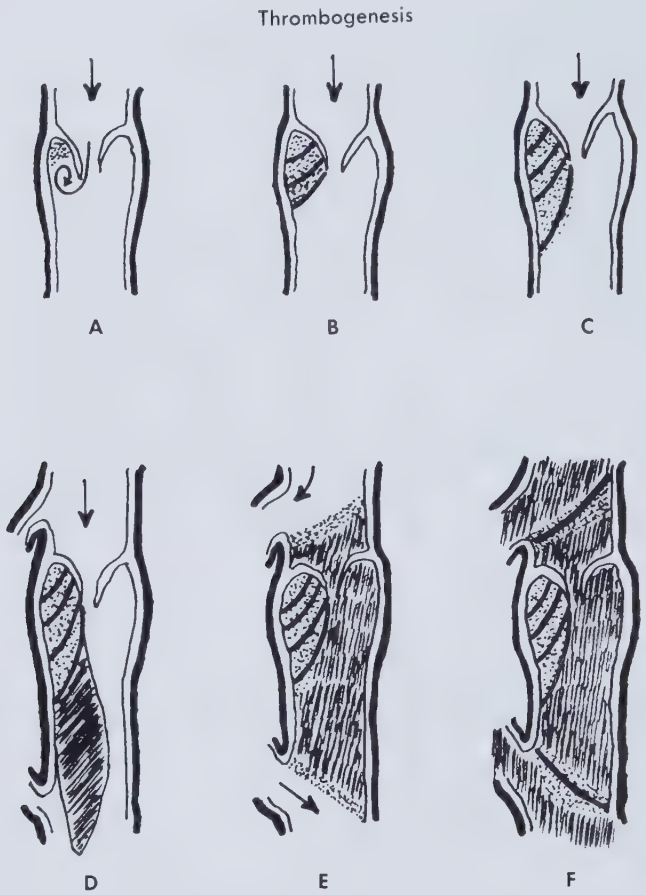

Fig. 11-1. **A,** Platelet aggregation in valve pocket. **B,** Fibrin deposition. **C,** Enlargement of platelet fibrin clot. **D,** Red thrombus in fibrin mesh. **E,** Total obstruction of vein with propagation. **F,** Blockage of collaterals.

flow may induce the formation of coarse fibrin mesh that entraps red cells, forming an intravascular clot and further stasis in the affected area.

If the thrombus becomes large enough to occlude the vein, it will propagate in both directions until it reaches a tributary with sufficient flow to prevent the soft red clot from forming further. At this point the layering process is repeated. Should this tributary become occluded, further propagation of soft clot will continue until another area of increased flow and decreased coagulability is encountered. The thrombotic process activates the plasmin fibrinolytic system and the balance between clot formation and lysis determines the eventual outcome of the thrombosis. If the thrombus is not completely lysed, it becomes organized, and later the vessel recanalizes with destruction of the valves. Clot that has not yet organized or adhered to the vein wall may break free, forming an embolus.

Due to the relatively small size of the platelets, they tend to remain in the periphery of a streamline flowing column of blood and accumulate in areas of stasis and turbulent eddy flow. One would therefore expect on this basis to find thrombus formation in the pockets of venous valves, areas of bifurcation, and stagnation. The large soleus venous sinuses that drain the calf muscle are in a

dependent position during recumbency and are a particular area of stasis in the relatively immobile bedridden patient. Although most pulmonary emboli of significance come from the femoral and iliac veins, the early thrombosis in most instances has been found by the ^{125}I fibrinogen technique to be in the calf veins.[33]

At present there is no evidence that hypercoagulability of the blood or stasis of flow alone causes local thrombus formation. Local trauma to the vessel wall, antigen-antibody complexes, endotoxin, or other elements that cause platelet aggregation and release are probably the initiating factors. Secondary red thrombus may form on such a nidus as a result of decreased rate of blood flow in the area. Patients with increased coagulability or with an impaired fibrinolytic system are more likely to form a thrombus.

Diagnostic procedures

The clinical manifestations of deep vein thrombosis are produced either by obstruction of major veins or by an inflammatory response produced by the thrombus in the immediate local area. As a result of rich collaterals or lack of inflammation, a patient may have extensive thrombi present in the legs without symptoms, particularly if he is in bed. Therefore the accurate diagnosis of the presence of venous thrombus in the legs depends more on sensitive and precise methods than clinical examination. In the past two decades, progress has been made in developing techniques for the early detection of deep vein thrombosis. This has allowed the identification of patient populations with increased frequency of thrombosis, documentation of the progression of the disease process, and the evaluation of methods of prevention and treatment.

Phlebography. The anatomy of the venous channels in the leg can be demonstrated radiologically. Ascending phlebography is performed by slowly injecting 50 to 100 ml of iothalamate meglumine or other suitable contrast medium through a dorsal foot vein. The patient is placed in a semiupright position, supporting his weight on the contralateral foot. An ankle and/or thigh tourniquet may be used to distend the venous system and force the contrast material into the deep leg veins. Fluoroscopic monitoring during injection is essential to study the normal flow pattern and to increase the efficiency of spot filming. Image intensification is necessary for minute detail. A Valsalva maneuver or a more rapid injection will allow good visualization of the thigh and iliac systems. Elevation of the legs will also aid visualization of the iliac veins.

The four cardinal signs of venous thrombosis are (1) constant filling defects, (2) an abrupt termination of a dye column, (3) nonfilling of an entire venous system or portions thereof, and (4) the diversion of flow to superficial channels. Common causes for artifacts are underfilling, dilution, and layering of the contrast material as it flows through vessels. It is frequently difficult to fill the soleus sinuses, since they drain the calf musculature primarily and small thrombi in these veins may be overlooked. The venous system should be flushed with saline solution immediately following phlebography to prevent thrombophlebitis secondary to irritation by the contrast material.

Percutaneous femoral injection may also be used for greater detail of the pelvic veins. Intraosseous injection may be performed using a bone marrow needle for injection if a site for intravenous injection is not available. This may require general anesthesia if multiple sites of injection are required.

Phlebography has become the final arbiter for the diagnosis of venous throm-

bosis. However, it is quite expensive, at times has painful side effects, and is logistically cumbersome. It is indispensable in evaluating clinical thrombophlebitis, chronic leg swelling, and the extent of venous involvement in cases of pulmonary embolism.

Ultrasonic Doppler flow meter. In 1967 Strandness et al.[62] described the use of the ultrasonic Doppler flow meter to measure the alterations in velocity of blood flow that occur in veins containing thrombi. The instrument emits a sound beam that is directed percutaneously through the underlying vein. When the ultrasound waves encounter moving particles in the bloodstream, their frequency is shifted in an amount proportional to the flow velocity. The shifted and nonshifted frequencies are then mixed to produce a beat that may be amplified and recorded by machine or that can be heard. The procedure may be used to study the deep veins of both legs under similar conditions. The veins examined include the common femoral, superficial femoral, popliteal, and posterior tibial veins. In normal individuals there is a change in the velocity of venous flow with respiration that can be detected by recording over the common femoral vein. With deep inspiration, the velocity decreases as intra-abdominal pressure increases. Occlusions proximal to the common femoral vein produce a continuous velocity signal not appreciably influenced by respiration or a Valsalva maneuver. If the vein is completely occluded, no flow signals will be obtained. Flow signals in the leg veins can be augmented by sudden forceful compressions of the calf muscles or dorsiflexion of the foot. Both legs must be examined under identical conditions and the results compared.

This method is noninvasive, inexpensive, and has the advantages of easy portability, simplicity, and the absence of trauma. It requires considerable experience in order to obtain maximum reliability and has not yet been subject to quantification. The technique may prove to be valuable for the diagnosis of thromboses involving the iliac, femoral, and popliteal vessels, but frequently fails to show venous occlusions confined to the small veins of the calf. Ultrasound may prove valuable in following patients with chronic venous insufficiency. The technique cannot detect clot when large patent collaterals are present or when only tributaries are involved by thrombosis.

Plethysmography. With deep inspiration, pressure in the inferior vena cava is increased, venous return from the legs is reduced, and venous blood volume in the legs is increased. Expiration produces the opposite effect. The expansion and contraction of leg volume with deep inspiration and expiration has been studied by Wheeler and Mullick[68] using impedance plethysmography. Since blood is an excellent conductor of electricity, the impedance to passage of an electric current through tissue varies inversely according to the amount of blood in the electric field. A current of less than 1 ma is applied to the leg through a pair of circumferential electrodes placed about the calf. A second pair of electrodes is connected to a Kelvin bridge circuit that is balanced with an internal resistance equal to that of the patient. Voltage changes may then be read directly from a volt meter and appropriately recorded. The test is performed with the patient in a supine position with his legs in slight external rotation and knees flexed about 20 degrees. The patient should be relaxed and breathing comfortably. He is then instructed to hold his breath for 2 or 3 sec and slowly exhale. The maximum respiratory impedance excursion at the end of breath holding is depressed in

those with thrombophlebitis, and the overall changes in the impedance tracings are more gradual in the involved leg. Bilateral and sequential tracings for comparison are imperative. Maximum respiratory impedance excursion cannot be measured accurately in patients who cannot voluntarily take a deep breath. However, by using a venous tourniquet on the upper thigh, one can compare the rate of impedance change following release. This has proved an accurate addition to the technique.

Impedance plethysmography is noninvasive and does not produce discomfort. The portable instruments are relatively modest in cost. Therefore the technique may be valuable as a screening test for the presence of clinically significant thrombi and particularly in the detection of clots involving the iliofemoral system. However, many limbs may show equivocal results.

Strain-gauge plethysmography may also be used to measure the rate of decrease in leg volume following release of a venous thigh tourniquet.

Barnes et al.[1] found a 5% incidence of false negative diagnoses and 18% false positives in 41 patients evaluated radiologically. Plethysmography may be used as an adjunct in diagnosis and a method to study long-term hemodynamic changes caused by venous thromboses and is valuable in following patients with postthrombotic venous disease.

^{125}I fibrinogen test. The ^{125}I fibrinogen technique takes advantage of fibrin deposition on a clot during propagation and is most sensitive in detecting small asymptomatic thrombi in the small calf veins. An iodine solution is given the day before and continued daily for 4 weeks to saturate the thyroid gland and thereby minimize its uptake of radioactive iodine. Scanning may be performed approximately ½ hr after administering 100 to 150 μC of ^{125}I-labeled fibrinogen intravenously through an arm vein. The scanning procedure can be repeated for approximately 1 week following a single dose of labeled fibrinogen. Employing a lightweight portable isotope localization monitor, this technique may also be used with no major inconvenience to the patient and can be accurately performed by a trained technician. The patient is placed in a supine position with his legs elevated to a constant level in order to decrease the blood volume and reduce the background of radioactivity to a minimum. Readings are taken from previously marked 2-inch intervals over the superficial femoral vein from the inguinal ligament to the knee and over the posterior, lateral, and medial aspects of the calf from the popliteal space to the ankle. An initial reading is taken on the anterior chest over the heart in an area of maximum radioactivity. This is recorded as 100% and leg readings are recorded directly as a percentage of the heart count. Localized elevations in radioactivity of 20% or more are considered positive evidence for thrombus formation (Fig. 11-2).

Because of the difficulties involved in formulating a suitably pure fibrinogen product and in developing a reliable tagging procedure and because of the possible risk of transmitting viral hepatitis, this technique has been limited to research studies in the United States. By obtaining blood for fibrinogen from selected donors who have no known history of hepatitis and who are Australian antigen free, the risk of transmitting hepatitis should be minimal. The test may not be accurate in the upper thigh or iliac regions because of increased muscle mass, large vessels, and close proximity to the urinary bladder, but its degree of sensitivity in the lower legs makes it a valuable investigative method for distin-

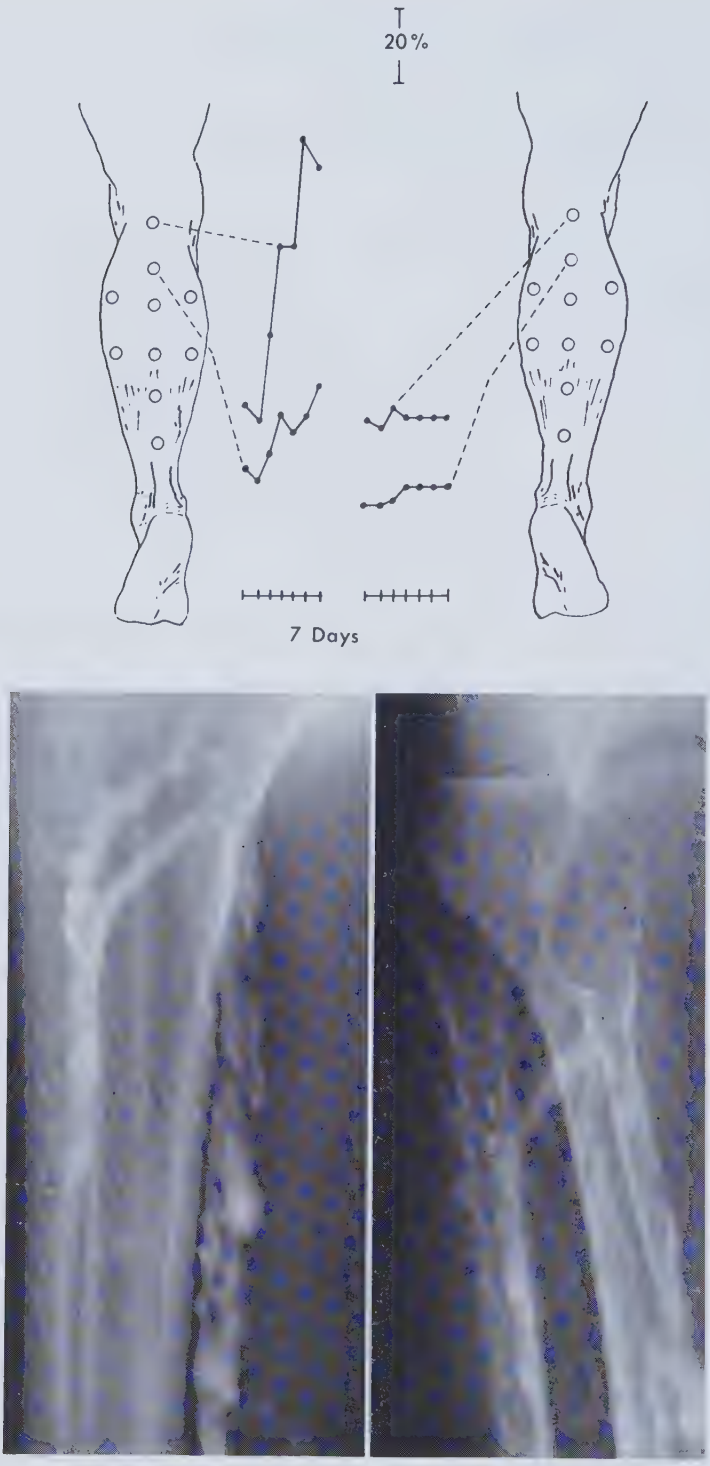

Fig. 11-2. Positive ^{125}I fibrinogen test in patient with asymptomatic deep vein thrombosis of left calf. Phlebogram demonstrates large thrombus present in left popliteal vein.

guishing the patient with increased risk of developing deep vein thrombosis, delineating the mechanisms involved in early deep vein thrombosis, and evaluating preventive therapy.

The ^{125}I fibrinogen test results agree with those of ascending phlebography[32] (Fig. 11-2) in 80% to 90% of patients, and scanning may be more sensitive than phlebography in diagnosing calf vein thrombosis. Hematomas, edema, inflammation, and trauma of the extremities may cause false positive results. False negative results are rare and are usually the result of thrombophlebitis that is present prior to injection of the ^{125}I fibrinogen. The test becomes positive 24 to 48 hr before clinical symptoms appear, and many clots detected by this test lyse spontaneously without symptoms ever occurring. Of the thrombi demonstrated by this technique, 95% are in calf veins. Kakkar[32] reviewed his experience in 935 patients of whom 248 (24%) had positive ^{125}I fibrinogen tests. In 56 patients the thrombus propagated into the popliteal vein. Of these, nine developed pulmonary embolism. In the remaining 76% who had normal scans there were no pulmonary emboli. This would indicate that large thrombi that embolize from the femoral and iliac systems either propagate from calf thrombi or form concomitantly. Similar correlations with chronic venous insufficiency have not been made.

Certain high-risk groups of patients have been evaluated using the ^{125}I fibrinogen test. These include patients with myocardial infarction, stroke victims, and patients who developed heart failure. Patients with varicose veins, severe illness, or an age greater than 70 years are also at increased risk. The most thoroughly studied group of patients has been those undergoing operation. Kakkar,[33] using the ^{125}I fibrinogen test, studied 469 consecutive patients aged 40 years or more who were undergoing elective operations. He found an overall incidence of deep vein thrombosis of 27.8% and a higher incidence in the older patients undergoing major operations. Fifty patients with hip fractures had a much higher incidence of 54%. Gallus et al.[24] also noted a high incidence of thromboses in patients undergoing operation for hip fracture and those with cancer, although the overall incidence was lower (16%).

Therapy

When deep vein thrombosis is demonstrated or suspected, therapy is directed toward preventing the propagation and embolization of the existing thrombus, maintaining adequate venous return from the legs, and preventing further damage to the venous valves.

Anticoagulation. Heparin and nicoumalone were shown by Barritt and Jordan[2] to be effective in preventing recurrent pulmonary emboli in a controlled prospective clinical study of 35 patients. Ten of 19 patients in the untreated group developed recurrent emboli and five died. There was one death and no recurrent emboli in the 16 treated patients. The most frequently used anticoagulants are heparin and warfarin (Table 11-1).

Heparin's anticoagulant action is immediate when given intravenously, its half-life is predictable, and the dosage can be regulated by the Lee-White clotting time or more accurately by the activated partial thromboplastin time. Minor bleeding episodes can be controlled by withholding therapy. However, since heparin is a strongly acidic mucopolysaccharide, its anticoagulant action may be reversed promptly milligram per milligram by slow intravenous injection of

Table 11-1. Therapy of deep vein thrombophlebitis

	Heparin	Warfarin
Approximate dose	30,000 units/day intravenously (continuous infusion or intermittent at 4, 6, or 8 hr intervals)	2.5 to 15 mg/day orally
Onset of action	Immediately	3 to 6 days
Dosage regulation	Lee-White clotting time 20 to 60 min; partial thromboplastin time 60 to 100 sec	Quick prothrombin time 10% to 30% of normal
Length of therapy	8 to 10 days	6 weeks to 6 mo
Antagonists	Protamine, mg/mg < 100 mg/hr	Vitamin K_1, whole blood

an equivalent amount of protamine sulfate, a basic protein of low molecular weight that is rich in arginine. No more than 100 mg of protamine should be given over a short period, since large doses of protamine may also act as an anticoagulant. An excellent review of the pharmacologic and clinical aspects of heparin therapy was given by Wessler and Gaston[66] in 1966. When using continuous intravenous infusion of aqueous heparin, the Lee-White clotting time should be maintained at 20 to 60 min or the activated partial thromboplastin time between 60 and 100 sec or 1½ to 2 times the control level. Under these conditions the recurrence of thromboembolism has been reported as 3% and the occurrence of bleeding less than 10%.[3, 11] The dosage of heparin required to maintain these levels is usually over 30,000 units/24 hr. Heparin may also be injected intermittently at 4, 6, or 8 hr intervals and similarly monitored 2 hr prior to the next injection. The amount of heparin required for this technique is approximately the same. Thromboembolic complications are comparable with either method; however, a controlled randomized study would be required to demonstrate the difference in recurrent thromboses or bleeding. It is most important to maintain adequate heparin levels for 8 to 10 days to allow time for the thrombus to become fixed to the vein wall. Heparin may be used subcutaneously, but control is more difficult because of variation of absorption. Intramuscular injections of any kind should be avoided during heparin therapy.

For long-term maintenance on an outpatient basis, oral anticoagulants are much more convenient for the patient but require several days to achieve their therapeutic effects. These drugs produce anticoagulation by reducing the effect of vitamin K–dependent clotting factors. Warfarin has become the leader in the group, although phenindione, phenprocoumon, and bishydroxycoumarin act in similar fashion. They should therefore be begun during heparin therapy at the usual moderate daily dose, e.g., warfarin, 10 to 15 mg, since this brings about depression of clotting factors VII, IX, X, and II at the same rate as large loading doses and decreases the incidence of overdosage. The daily dose may be monitored by the Quick prothrombin time and should be maintained between 10% and 29% of control activity. A prothrombin time less than 10% of control markedly increases the incidence of hemorrhage, and a range over 30% increases the incidence of recurrent thromboembolism.[8] In case of hemorrhage, oral anticoagulants can be counteracted by oral or parenteral vitamin K_1. With normal liver function, vitamin K_1 produces some effect on the prothrombin time within

2 hr and may return the prothrombin time completely to normal within 24 hr. Extreme caution should be taken when treating patients with liver disease. Transfusion will also reduce the effects of warfarin but does not alter the heparin response. In properly treated patients, thromboembolic complications occur most frequently in the first 2 weeks; however, 6 weeks to 6 months of anticoagulation therapy for thromboembolism is recommended. Abruptly stopping oral anticoagulant therapy does not increase the incidence of recurrent thromboembolism.

The list of drugs interacting with the coumarin derivatives is too long for the physician to remember, and the effects may be unpredictable, particularly if several interacting drugs are given simultaneously. Koch-Weser and Sellers[38] in an extensive review offered the following recommendations:

1. The physician should know *all* medicines taken by the patient.
2. No medicines should be taken under any circumstances without consultation with the physician controlling the anticoagulant therapy.
3. Patients on coumarins should not take barbiturates, chloral hydrate, chloramphenicol, ethclorvynol, glutethimide, nonsteroid anti-inflammatory agents, salicylates, phenyramidol, or quinidine.
4. All medication alterations should be kept to a minimum, and all new drugs should be regarded with suspicion.

Contraindications to anticoagulant therapy include bleeding diatheses, severe hypertension, acute ulceration or bleeding lesions, or recent central nervous system operations. Inadequate laboratory facilities or inadequate cooperation by the patient should also be considered a contraindication because inadequate control of these drugs may lead to serious complications.

Fibrinolytic therapy. Streptokinase and urokinase have been used in an effort to lyse the acute thrombus by activating plasminogen. Kakkar et al.,[34] using the ^{125}I fibrinogen test to diagnose thrombosis, showed that streptokinase was more effective for complete thrombolysis than heparin as shown by posttreatment phlebograms. The success of this therapy depends on early diagnosis. Clots over 5 days old do not respond to streptokinase nearly as well. LeVeen and Diaz[39] also showed good clot lysis of early thrombosis using streptokinase but emphasized that it needed to be followed with heparin, since there is a predisposition to thrombosis after therapy. Hemorrhage from operative sites, needle punctures, and other areas of trauma as a result of streptokinase and urokinase makes these drugs impractical in postoperative patients. Streptokinase, an enzyme produced by hemolytic streptococci may induce antibody formation and therefore may be ineffective if used more than once. Urokinase extracted from urine avoids this problem but is very expensive to obtain. The effects of these drugs may be reversed readily with epsilon amino caproic acid.

Thrombectomy. In an attempt to maintain venous patency in iliofemoral venous thrombosis, numerous attempts have been made at thrombectomy. They have met with varying amounts of success, and only a few authors have reported preservation of venous valves following the procedure. The most important factor in maintaining the valve system is probably early thrombectomy. In a review of the literature in 1965, Smith[59] reported that patients whose symptoms lasted less than 3 days had the best chance of excellent results from the surgical procedure. Once inflammatory changes have occurred in the vein wall secondary to the thrombus there is probably no benefit from thrombectomy over anti-

coagulant therapy in preventing chronic venous insufficiency. The one instance where thrombectomy is the treatment of choice is phlegmasia cerulea dolens, or venous gangrene. In this instance the total venous outflow of the extremity is obstructed and unless the obstruction is relieved and blood flow restored, the limb may not be salvaged.

Prevention

Although anticoagulation is known to be an effective method of treating deep vein thrombosis, the overall morbidity and mortality of thromboembolic disease has not significantly changed in recent years. It has been estimated that less than 10% of the autopsies performed proved pulmonary emboli had a definite clinical diagnosis prior to death,[6] and that deep vein thromboses were diagnosed clinically with approximately the same frequency in this group of patients. In patients confined to bed, edema of the leg is not usually detected unless the thrombus has occluded the common femoral vein. More recently, using the sensitive ^{125}I fibrinogen test, Flanc et al.[22] found that only 50% of the deep vein thromboses detected by the ^{125}I fibrinogen technique could be detected clinically. In addition, the ^{125}I fibrinogen test was positive 24 to 48 hr before clinical signs appeared. With this high incidence of silent disease, any improvement in overall morbidity and mortality must be directed to preventive measures.

In the past many attempts were made to reduce the incidence of postoperative deep vein thromboses by decreasing the stasis of blood in the legs during and after operation. Rosengarten and Laird[51] and Rosengarten et al.[52] found in recent, well-controlled studies monitored by the ^{125}I fibrinogen technique that elastic or compression stockings and leg elevation were ineffective in decreasing the incidence of deep vein thrombosis.

Attempts have been made to increase the blood flow through the soleus venous lakes, since this is the primary location for initial clot formation in most patients. Doran et al.[16] in 1964 demonstrated large decreases in the velocity of venous blood flow during operation by injecting $Na^{24}Cl$ into a foot vein and measuring the circulation time to the groin. By stimulating the calf muscles during operation with an intermittent galvanic current, they were able to return blood flow to normal. Browse and Negus[4] using their technique reduced the incidence of deep vein thromboses as determined by the ^{125}I fibrinogen test from 20.9% to 8.2% in a prospective study on 110 patients using the patient's opposite leg as a control. Intermittent compression of the leg during surgery as well as passive intraoperative exercises have been found to be effective in reducing early postoperative thrombophlebitis.

These studies have been aimed at the intraoperative period, which represents a small fraction of the surgical patient's hospital stay. Tsapogas et al.[63] randomly studied 95 patients using extensive prophylactic measures throughout the postoperative course and reduced the incidence of ^{125}I fibrinogen–determined deep venous thrombosis from 14% to 4%. He used good-quality below-the-knee elastic stockings fitted prior to the operation and worn throughout the hospital stay. The foot of the patient's bed was elevated 30 degrees in the recovery room and throughout the postoperative period. Early postoperative ambulation was encouraged, but sitting or standing with the legs in a dependent position was prohibited. A program of passive and active exercises of dorsal and plantar flexion

during bed rest was instituted. Until further evidence is available such a program, including intraoperative intermittent leg compression or calf muscle stimulation, seems advisable, particularly in high-risk patients.

Because adequate ambulation, muscle exercise, and prevention of stasis have not been uniformly effective in preventing thromboembolism and require an excessive amount of work by hospital personnel, attempts have been made to reduce the coagulability of the blood during and after operation. Anticoagulation has not been widely accepted for this purpose for two reasons: (1) the increased incidence of bleeding during and after operation and (2) a need for adequate laboratory facilities to monitor anticoagulation properly. Harris et al.[27] showed a reduced incidence of clinical thrombophlebitis in patients treated with anticoagulating doses of warfarin postoperatively. Pinto[50] carried out a prospective study to evaluate the effect of warfarin on venous thrombosis in patients undergoing hip operations. He monitored the patients by the ^{125}I fibrinogen test and found no difference in the control and treated groups. Since it is known that adequate anticoagulation with warfarin may require several days, early subclinical thromboses may not be affected; however, clinical manifestations may be prevented by this drug.

Sharnoff and DeBlasio[58] reported only one death from thromboembolic disease in 850 high-risk patients; these results were obtained after using subcutaneous heparin sodium, 10,000 units the night before operation and 2500 units every 6 hr until the patient was discharged. They reported two instances of bleeding attributed to heparin that were caused by inadvertent, incorrect administration. Williams[69] found this dosage of heparin in the preoperative and postoperative period to be significant in reducing postoperative deep vein thrombosis from 41% to 15% as diagnosed by the ^{125}I fibrinogen technique after major abdominal operations. Other workers using prospective studies have found similar reductions in ^{125}I-labeled thrombi using 5000 units subcutaneously preoperatively and every 12 hr thereafter (Table 11-2).[25, 35, 36, 46] At this dosage, routine coagulation tests have failed to show any significant abnormality, and hemorrhage has not been a problem. Gallus et al.[24] used 5000 units every 8 hr in a random study of 350 patients and reduced the incidence of positive leg scans after

Table 11-2. Incidence of postoperative deep vein thrombosis following low-dose subcutaneous heparin

	Total number of patients	Incidence of postoperative deep vein thrombosis detected by ^{125}I fibrinogen test			
		Control	%	Treated	%
Kakkar et al.[35]*	53	7 of 27	26	1 of 26	4
Kakkar et al.[36]*	78	17 of 39	42	3 of 39	8
Gordon-Smith et al.[25]*	150	21 of 50	42	11 of 100	11
Nicolaides et al.[46]*	244	29 of 122	24	1 of 122	0.8
Gallus et al.[24]†	350	19 of 118	16.1	2 of 108	1.9
Williams[69]‡	56	12 of 29	41	4 of 27	15

*Heparin, 5000 units prior to operation and every 12 hr thereafter.
†Heparin, 5000 units prior to operation and every 8 hr thereafter.
‡Heparin, 10,000 units 9 to 10 hr prior to operation and 2500 or 5000 units every 6 hr after operation.

elective operation from 16% to 1.9%. Trauma patients, particularly those with hip fractures, have not responded as well to this program.

It has been demonstrated that heparin enhances the inhibition of activated factor X in much lower doses than required to prevent the generation of thrombin[70] and also affects platelet aggregation.[47] Although the exact mechanism is unknown, these may be factors in the effectiveness of heparin. At the present time, low-dosage subcutaneous heparin administered as 5000 units every 8 or 12 hr beginning preoperatively appears to be the best potential preventive measure available to reduce thromboses by decreasing the coagulability of the blood.

Agents affecting platelet function have not been uniformly successful. Many trials using dextran 40 and 70 postoperatively have not shown a beneficial effect in preventing deep vein thrombosis. However, one randomized double-blind study of 900 patients by Jansen,[30] in which he used 500 ml of 5% glucose or 500 ml of dextran (either 40,000 or 70,000 molecular weight) during operation, showed a significant reduction in clinical thrombophlebitis (verified by phlebography) and pulmonary emboli following operations of 1 hr or less in duration. The overall reduction of thromboembolism was from 10% to 5% in the dextran-treated patients. They also demonstrated a postoperative increase in venous return from the legs secondary to dextran administration. A prospective randomized double-blind trial with aspirin, 600 mg prior to and 5 days following operation, revealed no significant difference in deep vein thrombosis as measured by the ^{125}I fibrinogen uptake test.[15] In patients undergoing hip arthroplasty, Salzman et al.[53] found aspirin, dextran, and warfarin to be equally effective in reducing clinical venous thrombosis from 34% to less than 15%. Further evaluation of drugs affecting platelet function for the prevention of venous thrombosis is needed.

PULMONARY EMBOLISM

As has been previously mentioned, there is a marked discrepancy in the clinical and postmortem data concerning thromboembolic disease, which would suggest that it is still grossly underdiagnosed. Since pulmonary embolism and infarction may produce a wide variety of clinical findings, it may mimic many other diseases. While an embolic episode may be catastrophic, producing shock and syncope or even cardiac arrest, it may also cause substernal chest pain, mimicking myocardial infarction, or may be quite subtle and nonspecific, or may not produce any symptoms.

Clinical diagnosis

The presence of the classic triad of hemoptysis, pleural friction rub, and thrombophlebitis is no longer adequate to make a diagnosis. Recent data by Sasahara et al.[55] showed that hemoptysis occurred in only 38% of 100 patients with pulmonary embolism that was documented by lung scan or pulmonary arteriogram, 34% had phlebitis, and only 18% had a pleural friction rub. The most common symptom in these patients was dyspnea, which occurred in over 80%.[54] Cough occurred in approximately 70% of the patients, and pleuritic pain in less than 60%. An increased pulmonary second sound, tachypnea (defined as an increase in respiratory rate to greater than 20/min), rales, and tachycardia (greater than 100 beats/min) were the most common physical findings,

occurring in from 65% to 80% of the patients. Low-grade fever was present in approximately 50%. From this wide spectrum of nonspecific clinical findings, the great majority of which could be present in any cardiopulmonary disorder, it is apparent that the physician's index of suspicion must be high in order to make an early diagnosis. In many cases the size of the embolus is not related to the symptoms produced. Any patient with unexplained dyspnea, chest pain, left ventricular heart failure, congestive heart failure, or chronic lung disease should be evaluated for the possibility of pulmonary embolus. Hildnex and Ormond[25] found that except for phlebitis no element of the history of physical examination favored or opposed pulmonary emboli.

Serum enzymes and other laboratory tests

Wacker et al.[61] proposed a triad of elevated lactic dehydrogenase, normal serum glutamic oxaloacetic transaminase, and elevated serum bilirubin to differentiate pulmonary embolus and infarction from other clinical entities. Although this pattern may lead one to perform further diagnostic studies, the absence of changes in these tests should not deter one from suspecting pulmonary embolus. Serum bilirubin elevation is frequently due to hepatic congestion accompanying right ventricular heart failure. The creatine phosphokinase level may be of value in differentiating myocardial infarction, but it has also been found to be elevated in some cases of pulmonary embolus. The white blood count is normal or slightly elevated to less than 15,000 in over 90% of the patients.[54]

Electrocardiography

The ECG findings in acute pulmonary embolus are usually transient and represent right ventricular heart strain. The QRS complex may show S waves in lead I and Q waves in lead III. These may be accompanied by a T wave in lead III and prominent S waves in the left precordial leads. There may be T wave inversion in the right precordial leads. S-T segment depression may occur in leads I and II and the left precordial leads. Complete or incomplete right bundle branch block may be present. A variety of arrhythmias have been described, and peaked P waves may occur in leads II and III. These various changes occur most frequently with large emboli and small ones associated with infarction, but they may be very transient in nature. Although they may be helpful in evaluating the clinical picture, they are not specific for pulmonary embolus and may be seen in a variety of other conditions, including chronic cor pulmonale, acute anterior myocardial infarction, pneumothorax, following a pneumonectomy, and in patients with chronic obstructive lung disease and severe pneumonia.

Radiology

In evaluating the chest x-ray films of 78 consecutive patients who were suspected of having pulmonary emboli and who were referred for angiography, Hildnex and Ormond[25] found an infiltrate in 69% of those patients with documented pulmonary emboli and in 41% of those without emboli. Atelectasis, pleural fluid, and pneumonia were found with equal frequencies in the two groups. A normal chest x-ray film or one showing congestive heart failure was found to be more frequent in patients without pulmonary emboli. Local areas of oligemia associated with a fullness in the hilum as described by Westermark[67] in 1938 may

be suggestive of a pulmonary embolus and may be helpful diagnostically if present (Figs. 11-3 and 11-4).

The characteristic cone-shaped infiltrate with its base on a pleural surface is helpful in diagnosing pulmonary infarction if present; however, infiltrates secondary to pulmonary embolus may not be characteristic and may resolve over 2 to 3 days. Abnormalities found via the history, physical examination, chest x-ray film, ECG, or serum enzyme analysis may make one suspect a patient of having a pulmonary embolus; however, these findings are nonspecific. Lung scans and angiography are required to make an accurate diagnosis.

Pathophysiology

The pathophysiologic changes that occur with pulmonary embolism are partly a result of vascular obstruction of the pulmonary arterial system and partly of changes in the gas-exchanging function of the lung. McIntyre and Sasahara[10] studied the hemodynamic status of 20 patients with pulmonary embolism who were free of prior cardiopulmonary disease. The estimated obstruction to the

Fig. 11-3. A, Supine chest x-ray film of an elderly patient. Lung scans: **B,** anterior view; **C,** posterior view; **D,** right lateral view; and **E,** left lateral view.

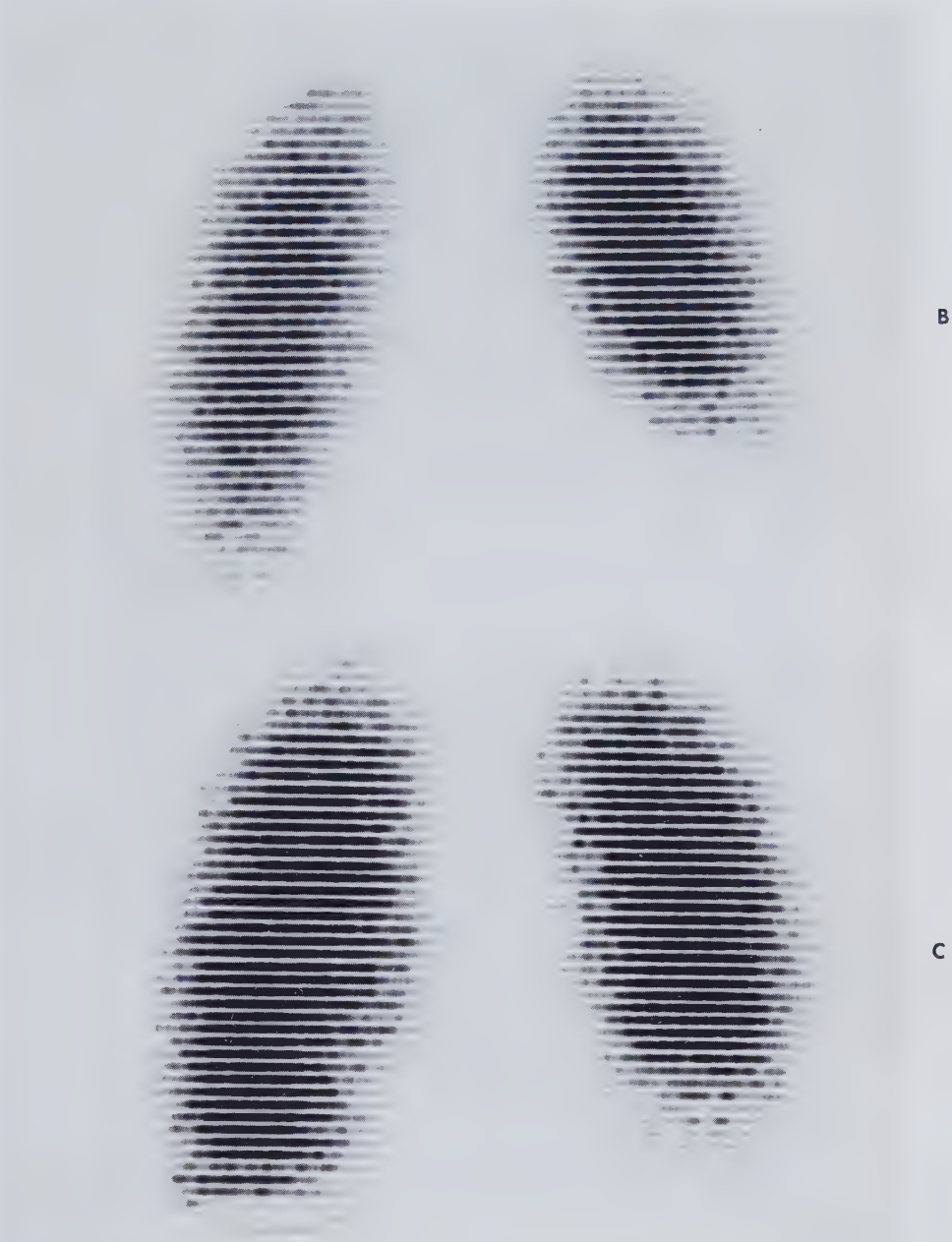

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Fig. 11-3, cont'd. For legend see opposite page.

Fig. 11-3, cont'd. For legend see p. 296.

pulmonary arterial system by angiography was 13% to 68%. The pulmonary arterial pressure was increased in 70% of the patients and correlated well with the amount of arterial obstruction. However, in no instance did it exceed 40 mm Hg. Patients with prior congestive heart failure or chronic obstructive disease were shown to tolerate pulmonary artery pressures greater than 40 mm Hg, but pressures of this magnitude were associated with right ventricular heart failure. Thus it would appear that the normal right ventricle cannot produce an arterial pressure over 40 mm Hg. The normal pulmonary circulation has a large capacitance that allows a total pneumonectomy or obstruction of greater than 50% of the vasculature without marked elevations in pulmonary arterial pressure. Elevated right atrial pressures were associated with pulmonary artery pressures greater than 30 mm Hg. Therefore one would expect an increase in central venous pressure with hemodynamically significant pulmonary emboli. Although serotonin and other vasoactive substances produced by platelets are thought to play a role in pulmonary artery hypertension secondary to pulmonary embolism in animal preparations, actual mechanical obstruction is felt to be the major factor in humans.

A

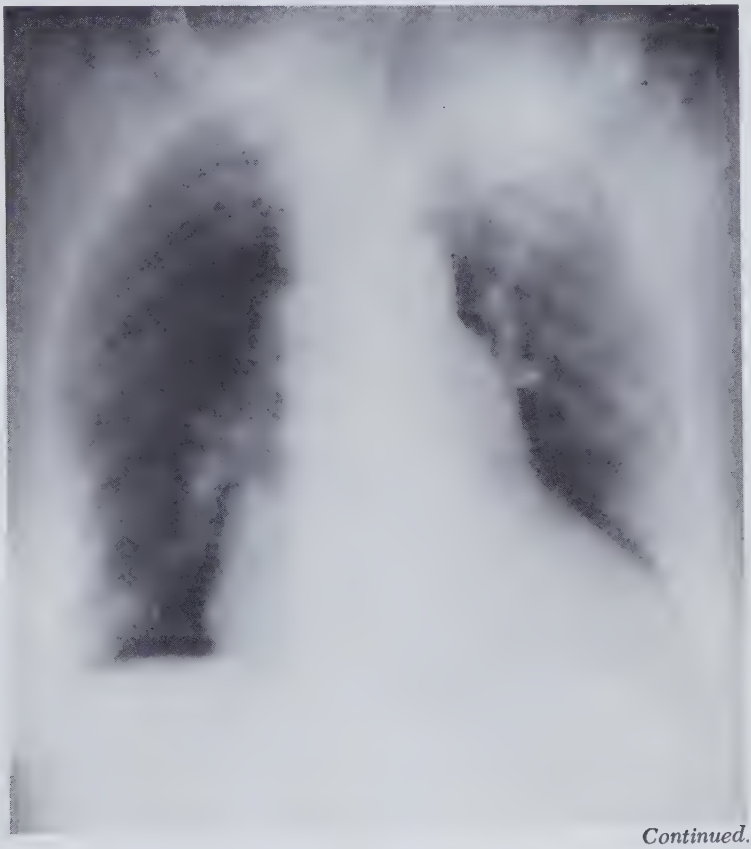

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Fig. 11-4. A, Ten days after films shown in Fig. 11-3 were taken chest x-ray film reveals widening of mediastinum, dilated pulmonary artery, cardiac enlargement, and relative radiolucency of lung fields. **B** to **E,** Corresponding lung scans show multiple defects compatible with pulmonary emboli.

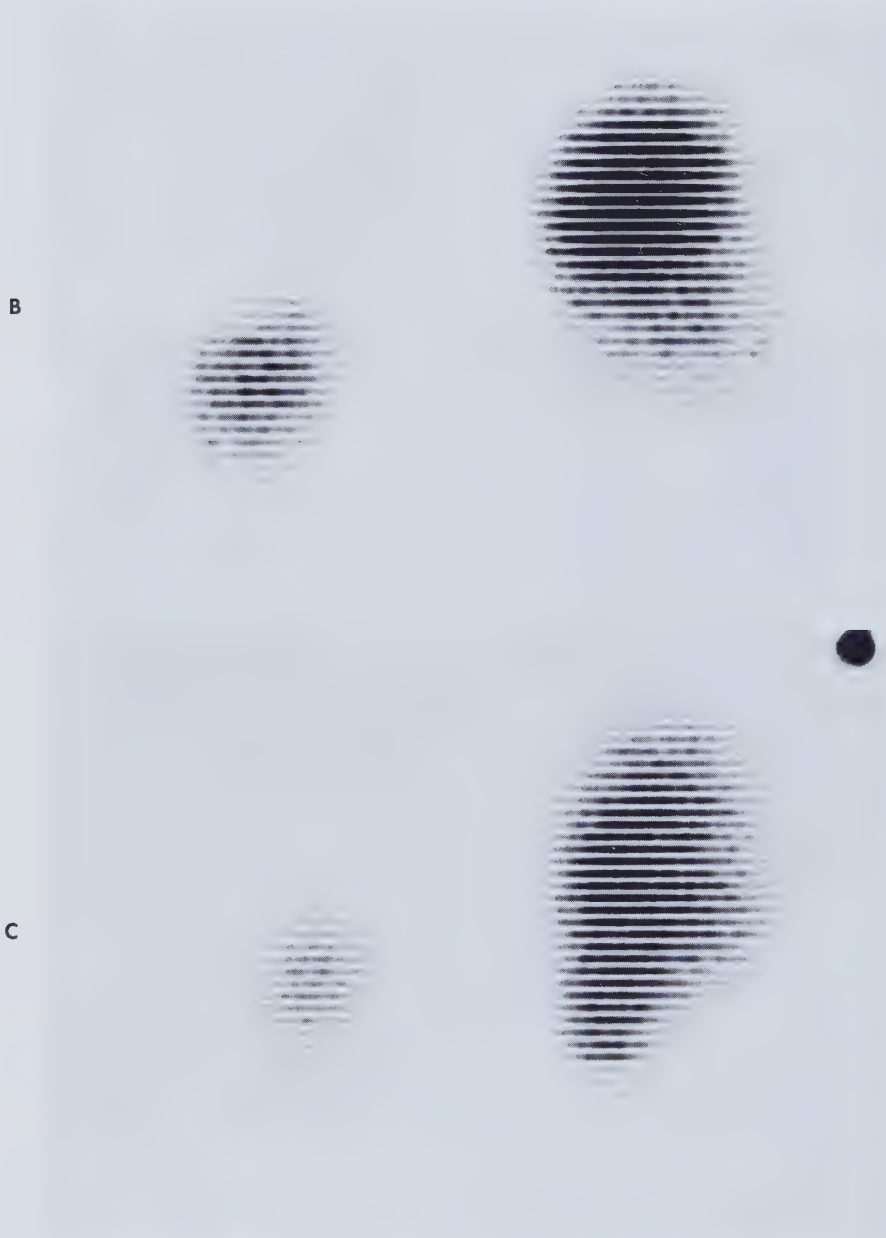

Fig. 11-4, cont'd. For legend see p. 299.

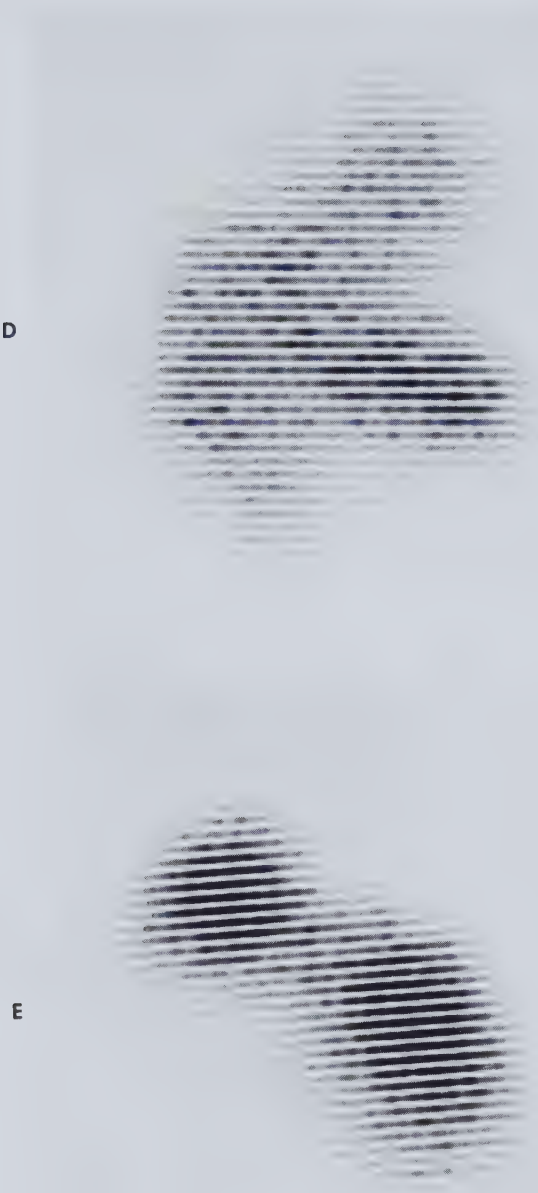

Fig. 11-4, cont'd. For legend see p. 299.

In 95% of the patients with pulmonary emboli but without previous cardiorespiratory disease, McIntyre and Sasahara[40] demonstrated a decrease in arterial oxygen saturation. This was also found in patients estimated to have as little as 13% vascular obstruction as calculated from pulmonary angiograms. If such patients who are hypoxemic on room air are then placed on 100% oxygen, arterial oxygen saturation will increase to 200 to 600 mm Hg.[56] This would indicate that although some patients show no evidence of venous admixture, others have a decrease in arterial oxygen saturation that may be secondary to abnormalities of the ventilation perfusion ratio or right-to-left shunting. Anatomic shunting may also be seen through bronchial veins and a patent foramen ovale when right atrial pressure is elevated. These communications are known to exist in approximately 20% of normal subjects and account for paradoxic embolization.

Pulmonary embolism by a single large clot that detaches from the popliteal, femoral, or iliac vessels and produces obstruction in the larger pulmonary arteries represents one end of the spectrum. Embolism to sublobar and smaller vessels is relatively more common; often these emboli are multiple. Microembolism that may be asymptomatic or produces chronic cor pulmonale is being recognized more frequently. The resolution of these emboli depends on their size and age at the time of impaction and the effectiveness of the fibrinolytic mechanisms within the lung. Fred et al.[23] studied the results of heparin treatment of acute pulmonary emboli by serial selective arteriograms in seven patients who had no evidence of coexisting cardiorespiratory disease. He found complete resolution by angiography in six patients within 7 to 19 days and nearly complete resolution in the remaining patient within 16 days. Similar results were shown by Chait et al.,[5] who demonstrated complete or almost complete resolution of emboli within 10 to 184 days in patients without cardiac or lung disease. Of 13 patients with cardiopulmonary disease, resolution of the embolus occurred in only one. Dalen et al.[12] studied 15 patients and found minimal angiographic and hemodynamic evidence of resolution within the first week, but found more normal pressure in the right heart and unmistakable angiographic resolution in less than 3 weeks.

Ellison and Brown[19] studied the fibrinolytic activity of the blood in patients with pulmonary infarction and pulmonary hypertension. They found no abnormality of fibrinolysis in those with pulmonary hypertension, including four with hypertension secondary to repeated pulmonary emboli, but in contrast found markedly reduced fibrinolysis in 9 of 11 patients with a history of pulmonary infarction.

Dunnill[17] studied pulmonary emboli in 263 autopsies. Pulmonary infarction was present only in those patients in whom there was complete occlusion of a pulmonary artery. It was most frequently seen in elderly patients with passive congestion of the lung, poor bronchial circulation, or concurrent pulmonary disease. Infarction was infrequent, however, and was nearly always associated with local pulmonary venous thrombosis. He postulated that pulmonary embolism is a frequent occurrence in normal individuals and that the lungs have a very efficient system for removing these clots. Patients who develop pulmonary infarction and chronic pulmonary hypertension have multiple factors that may prevent them from clearing the thrombi from their pulmonary vasculature.

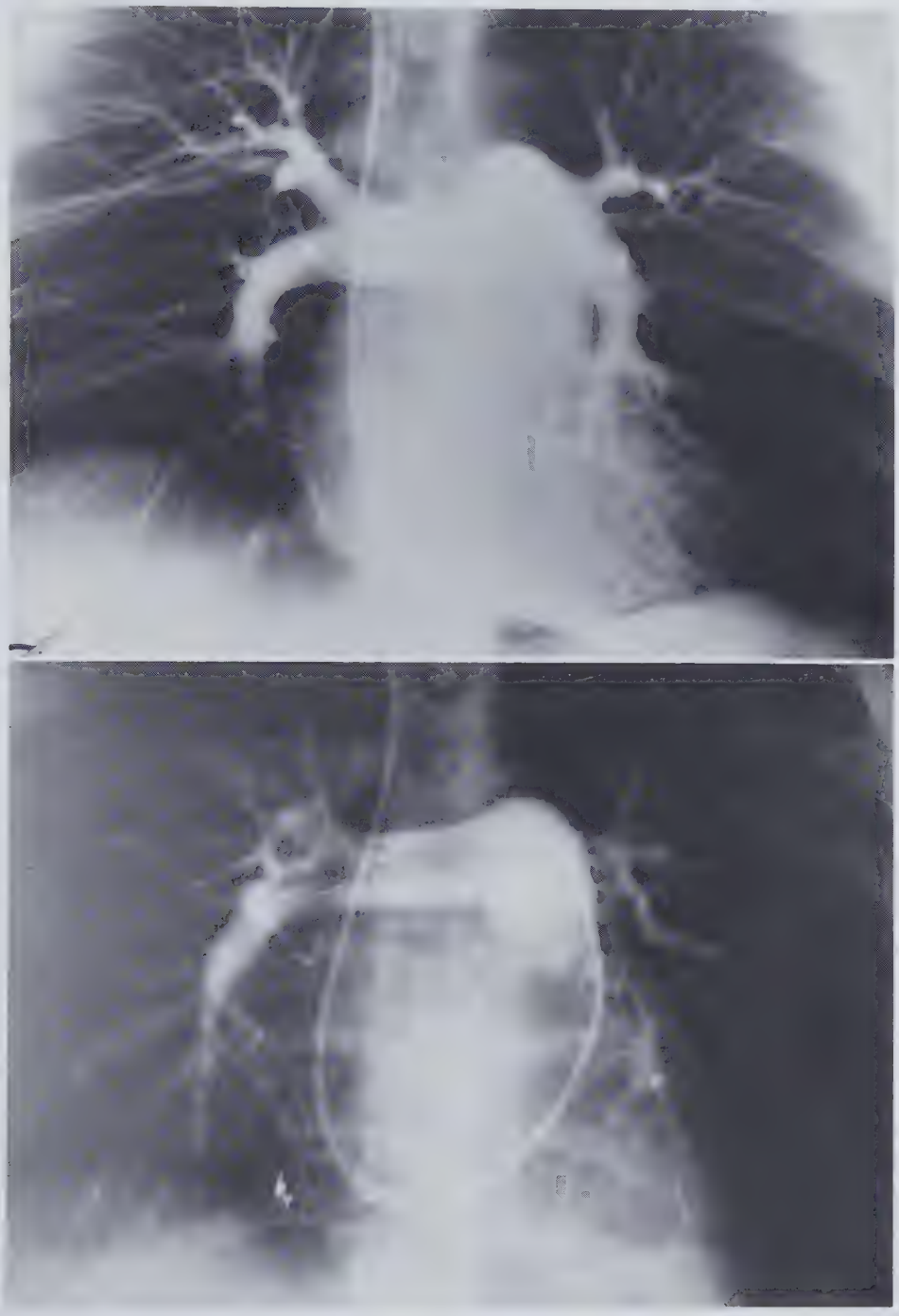

Fig. 11-5. **A,** Normal pulmonary angiogram. **B,** Angiogram shows large embolus in right and left main pulmonary arteries.

Pulmonary angiography

The recent development of angiography and lung scanning has allowed physicians to delineate pulmonary embolism more precisely. Pulmonary angiography is the most specific test available for the diagnosis of acute pulmonary embolism. A closed-tip angiographic catheter with multiple side holes may be inserted through an antecubital vein and under fluoroscopic control placed into the right heart or pulmonary artery. The cardiac output may be determined by the indicator dilution technique. Pressures in the pulmonary artery, right ventricle, and right atrium may be determined and should be correlated with the systemic arterial pressure. Contrast media may be injected into the right atrium, right ventricle, or main pulmonary artery. An injection of meglumine diatrizoate or other appropriate contrast media is made at a rate of approximately 20 to 30 ml/sec, and rapid sequence films are taken in the anterior posterior projection. The peak arterial phase was found to be at 4 sec, with a delay being noted in those patients with left ventricular heart failure, pulmonary hypertension, or a reduced cardiac index. The film sequence should be long enough to visualize the aortic arch and rule out a possible dissecting aneurysm.

In 13 patients with proved pulmonary emboli, Ferris et al.[21] demonstrated that filling defects were present in 48% and an arterial cutoff was seen in 27%. The main pulmonary artery was dilated and the number of small branches decreased in 17%. Although asymmetry in flow in areas of oligemia are very frequently found in pulmonary embolism, they may also be present in patients with congestive heart failure and chronic lung disease. The demonstration of intraluminal filling defects or cutoffs in the pulmonary arteries is necessary to make a definite diagnosis of pulmonary embolism (Fig. 11-5). In patients without evidence of coexisting lung disease, asymmetry of blood flow or oligemia has been used to diagnose probable pulmonary embolism. Patients with known lung or heart disease who have angiographic evidence of probable pulmonary embolism or uncertain filling defects and cutoffs are diagnosed as equivocal.

The risk of angiography is essentially the risk of right ventricular heart catheterization. The only absolute contraindication is a known allergy to the contrast media, but patients with recent myocardial infarction, ventricular irritability, and conduction abnormalities are considered to be in a high-risk group. Pulmonary angiography is essential to determine the exact location of thrombi in patients who may require pulmonary embolectomy. Patients with a positive lung scan and a corresponding infiltrate demonstrated on chest x-ray films may require angiography to differentiate pulmonary infarct from a primary inflammatory process (Fig. 11-6). The technique may be time-consuming and requires special x-ray equipment. Further refinement of the technique by magnification and cineradiography may increase its accuracy and be helpful in the diagnosis of multiple small pulmonary emboli.

Lung scanning

One of the functions of the pulmonary circulation is to act as a filtration system to prevent particulate matter from entering the systemic circulation. Lung scanning takes advantage of this function and records the distribution of intravenously injected radioactive particles that are trapped in the pulmonary vasculature. Macroaggregated iodinated ^{131}I–labeled serum albumin (MAA-^{131}I)

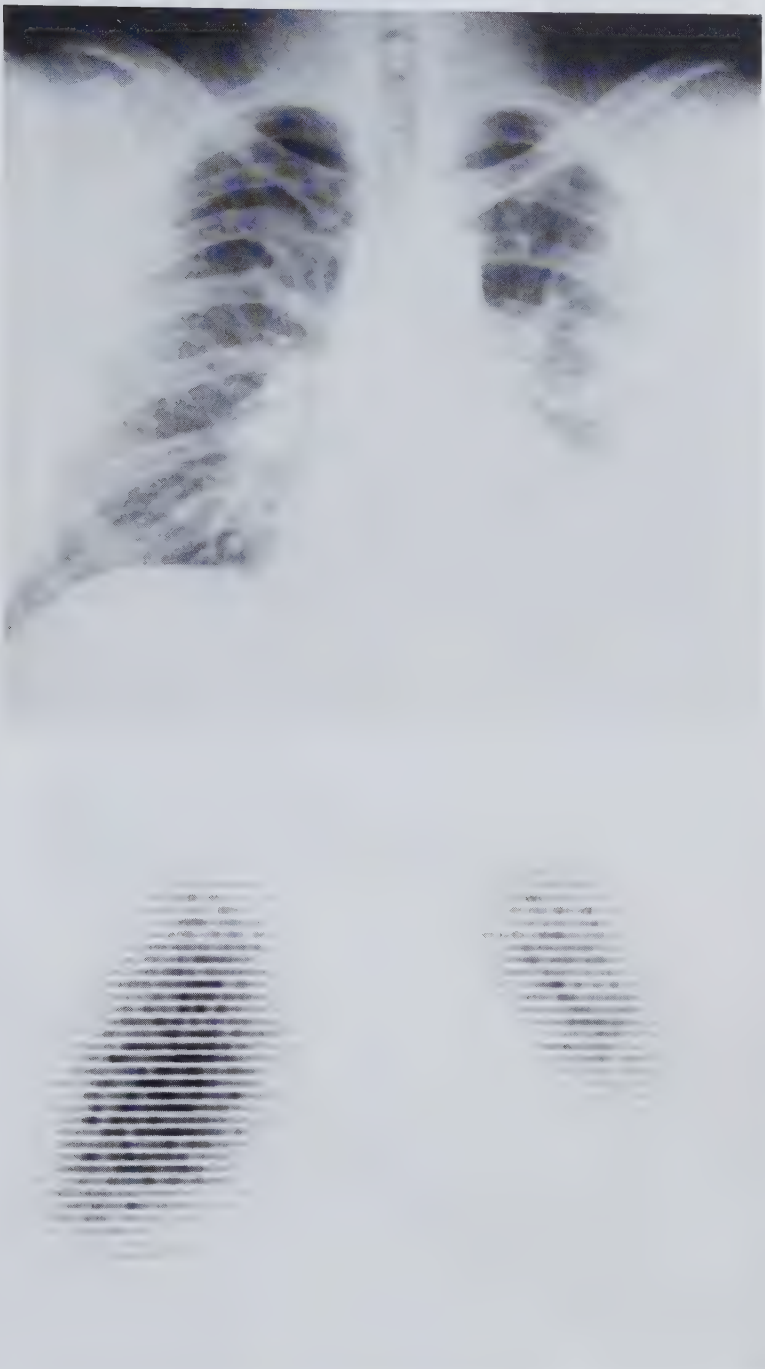

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Fig. 11-6. Patient with pain in left side of chest. **A,** Chest x-ray film demonstrates infiltrate at left base. **B,** Scan shows perfusion defect in same area. **C,** Arteriogram reveals embolus in anterior basal segmental artery.

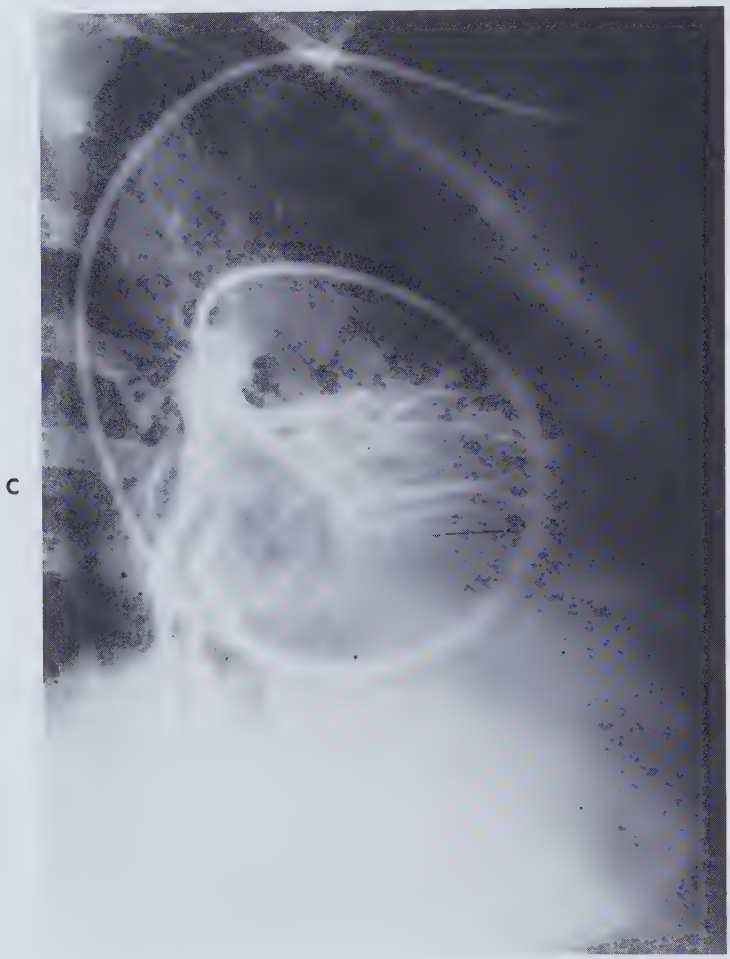

Fig. 11-6, cont'd. For legend see p. 305.

in particle sizes of 10 to 50 μ provides a suitable temporary arteriolar blockade in the pulmonary circulation. It is not antigenic and has a half-life of 5 to 10 hr. With scanning immediately following injection, 300 μC of MAA-^{131}I may be injected intravenously. Lugol's solution or intravenous sodium iodide should be given prior to injection in order to block the thyroid and reduce thyroid radiation. Lung scans may be obtained by a rectolinear scanner or more rapidly with a scintillation camera. Unless there is an anatomic right-to-left shunt, the infused MAA-^{131}I perfuses the lung, and scans demonstrate the distribution of pulmonary arterial flow.

Abnormalities in regional blood flow may be seen in a number of disease processes but are most commonly seen in pulmonary thromboembolism, chronic lung disease, and congestive heart failure. The regional blood flow in pulmonary embolism has been described by Wagner et al.,[65] who demonstrated areas of arterial occlusion presenting as regional defects corresponding to the artery's distribution. It is therefore necessary to take anteroposterior, posteroanterior, and

right and left scanning views in order to determine the anatomic segmental nature of the lesion (Figs. 11-3 and 11-4). In chronic lung disease the affected areas do not have segmental involvement, and in congestive heart failure the defects seem to be smaller and more numerous with decreased perfusion to the lower lungs. Since pulmonary emboli present as abnormalities of blood flow rather than ventilation, it is necessary to have a chest x-ray film taken at the time of the scan to rule out ventilatory disease as the primary source of decreased arterial perfusion. Johnson[31] reviewed the role of lung scanning for pulmonary emboli and found a 92% agreement of scanning with pulmonary arteriograms in 122 cases. He concluded that a negative scan excludes the possibility of major emboli. However, small emboli may not be detected. The false positive and negative rates were 11% and 16%, respectively.

A ventilation scan showing the distribution of inhaled radioactive gas has been used to demonstrate areas of the lung with poor ventilation. By injecting intravenously a saline solution that contains ^{133}Xe during breath holding, a lung perfusion scan may be obtained immediately. By then having the patient rebreathe in a closed oxygen system with a carbon dioxide absorber, the lungs may again be scanned. This time the distribution of radioactive xenon will demonstrate lung ventilation. This technique of combining perfusion and ventilation scanning may show marked discrepancies in local ventilation-to-flow ratios and will hopefully improve the sensitivity in differentiating pulmonary embolus from chronic obstructive lung disease or other lesions with impaired ventilation.

Lung scanning has proved to be an invaluable aid in the diagnosis of pulmonary embolus and has been associated with very low morbidity. Although it may not replace the arteriogram for preoperative evaluation of a massive pulmonary embolus, it is an excellent screening device that is very sensitive, although somewhat nonspecific. Because of its low morbidity, it may be repeated at intervals in following the progress of pulmonary embolus resolution. These properties make it extremely valuable in the assessment of the therapy and pathophysiology of the disease.

Therapy of acute pulmonary embolism

Therapy for acute pulmonary embolism may be divided into two components: (1) preventive measures (designed to prevent thrombus formation, propagation, and embolization) that include anticoagulation and venous interruption and (2) definitive therapy (removal of the existing emboli) by embolectomy and fibrinolytic agents. The preventive techniques are discussed under thrombophlebitis and should definitely be applied to those patients with a known high incidence of thromboembolic complications. Until other effective means of prevention are clearly established, serious consideration of full anticoagulation should be given to those patients with congestive heart failure, myocardial infarction, and chronic pulmonary disease and to elderly patients who will be bedridden over a long period of time, since the incidence of thromboembolic disease in these patients may be from 30% to 50%.

Anticoagulation. Patients with acute pulmonary embolus or infarction should be treated with anticoagulant therapy in a manner similar to those with deep vein thrombophlebitis. This mode of therapy has been effective in preventing the propagation of deep vein thrombi as well as pulmonary emboli while allowing

the body's natural defenses to proceed with lysis. Kistner et al.[37] studied 52 consecutive patients prospectively to determine the incidence of pulmonary emboli in cases of deep vein thrombosis documented by phlebography. Patients were followed with serial lung scans and chest x-ray films. In some patients pulmonary angiography was used to verify the diagnosis. All patients were treated with heparin and warfarin. Of the 46 patients treated for thrombophlebitis, 52% had pulmonary emboli, of which 75% were silent. Pulmonary emboli were found in approximately one third of those patients whose clots were below the knee and in 50% when the clots were in the veins of the thigh and iliac systems. Of five patients with saphenous–common femoral thromboses, four had pulmonary emboli. This demonstrates the need for adequate anticoagulation in patients with superficial thrombophlebitis of the thigh.

Venous interruption. Various surgical procedures have been developed to prevent pulmonary emboli by interrupting the venous channels between the area of phlebitis and the right heart. These procedures may become necessary in patients in whom anticoagulation is contraindicated, in whom emboli continue during adequate anticoagulation, with progressive pulmonary hypertension from recurrent pulmonary emboli, and with recurrent emboli from septic thrombophlebitis. The indications for inferior vena caval interruption are as listed.

I. Ligation or partial interruption
   A. Recurrent pulmonary embolization while patient is on therapeutic anticoagulation
   B. Pulmonary embolization in patient when anticoagulation is contraindicated
   C. Failure of previous vena caval interruption
II. Partial interruption
   A. Extensive pelvic operations or extensive trauma involving distal vena cava or iliac veins
   B. Emergency abdominal operation in patient with active thrombophlebitis or pulmonary embolus
III. Ligation
   A. Small recurrent pulmonary emboli while patient is therapeutically anticoagulated
   B. Septic emboli from pelvis or legs

The value of venous interruption is difficult to evaluate because (1) most reports are uncontrolled retrospective experiences, (2) actual documentation of the location and extent of thrombosis by venography is lacking, and (3) the morbidity and mortality of reported series is to a large extent the result of the patient's general condition at the time of operation rather than of the operative procedure. Crane[9] compared his results of femoral ligation with vena caval interruption and found a 10% failure rate with femoral vein ligation and a 5% mortality rate from further embolism, as opposed to 1% in both categories following vena caval ligation. The mortality of both procedures in patients with left ventricular heart failure was approximately 20%. In those with right ventricular heart failure, the mortality was 40% if treated with femoral ligation as opposed to a 50% mortality with vena caval ligation.

Because of its increased effectiveness in preventing recurrent thromboemboli, vena caval interruption has become the method of choice except in patients with severe cardiac disease (Fig. 11-7). The oldest method of interruption is complete ligation as advocated by Ochsner et al.[48] Long-range results were judged as excellent in 73% of the patients and no recurrent emboli were identified. They found that 50% of the patients had immediate edema of the legs but persistent

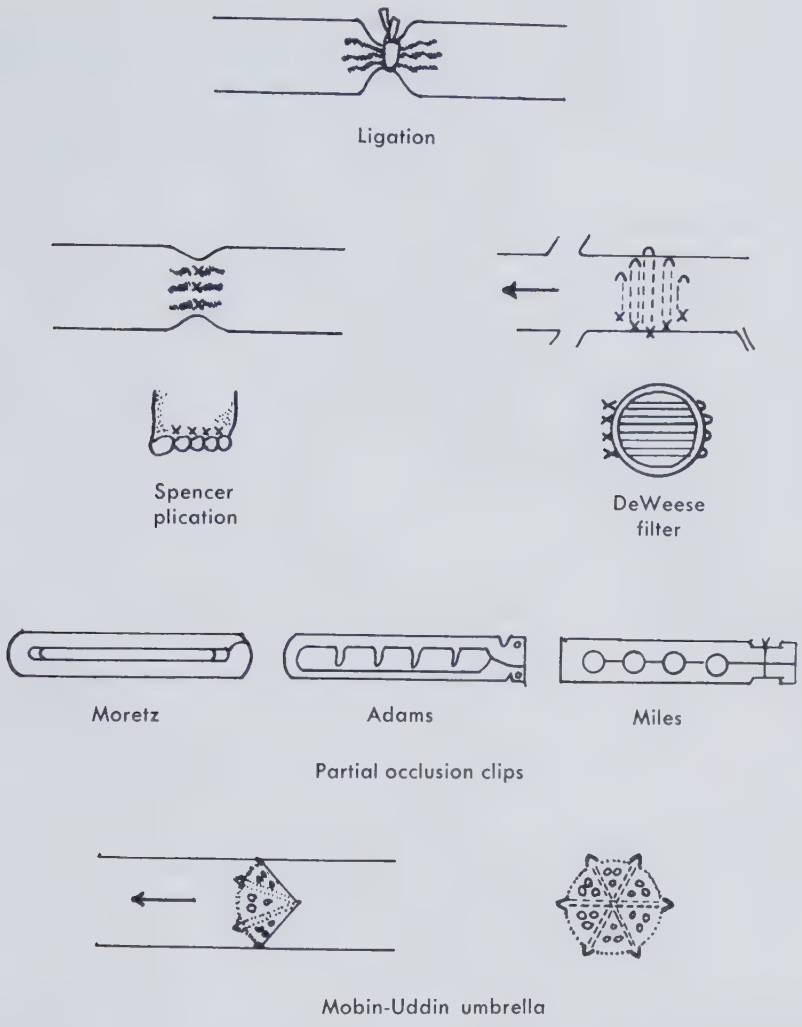

Fig. 11-7. Vena caval interruption techniques.

edema occurred in less than 5% of the patients. DeWeese and Hunter[14] designed the vena caval filter for partial interruption in order to prevent postligation thrombosis and postphlebitic syndrome of the lower legs. They used a network of fine arterial sutures across the vena cava just inferior to the renal veins, thus forming a trap to collect large emboli without impeding the flow from the lower extremities. Spencer et al.[61] used suture plication and Moretz et al.[44] used the application of a clip for partial occlusion of the inferior vena cava for the same reasons. Although these latter techniques are physiologically better in acute stages, they require more operative time to perform and will not prevent small pulmonary emboli. Ligation should be used in patients with recurrent small emboli or emboli from septic thrombophlebitis. All such techniques have been associated with a low incidence of recurrent pulmonary embolism.

Moretz et al.[45] reviewed their experience with 72 patients having partial occlusion by a clip and documented the ultimate fate of the clip site in 54

patients. Of these, 44 were fully patent, seven showed partial occlusion (of which four had previously been completely occluded 1 to 4 years earlier), and three were completely occluded. All methods of vena caval interruption have had similar long-term results in regard to venous insufficiency of the lower extremities. The incidence is directly related to the amount of venous thrombosis prior to operation. Rare cases of complete thrombosis inferior to the interruption with massive edema of the extremities have been reported. Anticoagulation should be used if possible to minimize thrombus propagation following interruptive procedures. Interruption should be performed just distal to major vena caval tributaries in order to prevent proximal propagation and possible recurrent emboli. Ligation of the ovarian or spermatic vein aids in preventing late embolism following ligation of the inferior vena cava.[15] Moran et al.[43] evaluated 54 patients, 29 of whom were treated by partial occlusion with a Teflon clip and 25 with ligation. They found no significant difference in the subsequent condition of the legs and no positive correlation between clinical findings and patency or occlusion of the inferior vena cava.

Because of the high mortality associated with inferior vena caval ligation in patients with significant cardiac disease, Mobin-Uddin et al.[41] developed a catheter technique for partial interruption of the inferior vena cava by an intracaval prosthesis. Its insertion can be performed through the internal jugular vein with local anesthesia. The umbrella-shaped device is positioned in the inferior vena cava, where it is opened and fixed in place by the pointed ends of its metal spokes. Insertion is monitored by fluoroscopy, and the prosthesis is placed below the renal veins. Complications of the procedure include insertion into a common iliac vein or renal vein, the inability to insert the catheter due to its size or abnormalities in the venous system, damage to adjacent structures during insertion, dislodgement of the prosthesis secondary to poor fixation to the vein wall, and retroperitoneal hematoma. Orvald et al.[49] reported leg swelling in 37% and phlebitis in 18% on long-term follow-up. Mobin-Uddin et al.[42] reported a 30-day hospital mortality of 19%, but this was attributed to the seriousness of the patient's original disease. Because of the low mortality of this procedure, it is probably indicated in patients who cannot tolerate general anesthesia. However, the long-term result of a large intraluminal metallic device is unknown. The possibility that the fixation prongs might erode the vessel wall and neighboring structures has made many surgeons reluctant to use the device in good-risk patients, particularly since these are the patients that do well with anticoagulant therapy. Further studies are needed before this question can be answered. Certainly the long-term results in comparison with other means of venous interruption need to be studied in a prospective randomized fashion.

Fibrinolytic therapy. Hirsh et al.[29] treated 18 patients with major pulmonary emboli using streptokinase therapy. In 12 of 16 patients studied angiographically, there was definite improvement within 12 to 48 hr. Clinical improvement was evident in 14 patients during this period. These results are in contrast to patients treated with heparin alone, whose angiograms frequently show no improvement for 4 to 5 days. Resolution of thrombi by fibrinolytic agents has been more complete in patients with recent emboli or a single isolated embolus than with multiple emboli. As a result of these and other promising data from studies using fibrinolytic agents, the National Heart Institute organized a multicenter controlled

clinical trial in 1967 to compare the thrombolytic effect of urokinase and heparin together with heparin alone for the treatment of pulmonary embolism.[57] Accelerated clot lysis was found as seen on scan and angiogram paralleled by a 30% decrease in mean pulmonary artery pressure in the urokinase patients as opposed to 4% in the heparinized group. After 5 days, there was no significant difference in the rate of lysis, and long-term results were the same in both groups. There was a definite hazard of bleeding from cut-down sites with urokinase therapy and the recurrence rate of pulmonary embolus was similar in the two groups. Because of rapid restoration in cardiac function and respiratory reserve with urokinase therapy, pulmonary embolectomy may not be as urgent with this form of therapy.

Pulmonary embolectomy. Patients with massive pulmonary embolus occluding over 50% of their pulmonary arterial tree may have right ventricular heart failure. This obstruction may produce decreased filling of the left ventricle and systemic hypotension. Decreased coronary artery pressure during right ventricular heart failure can lead to a vicious circle ending in the death of the patient unless the cycle is rapidly interrupted. Soloff and Rodman[60] plotted survival time in patients with massive pulmonary emboli. Only 40% of the patients survived 30 min and 30% for 2 hr. Approximately 20% survived for 6 hr. It is therefore apparent that any therapy to reduce this mortality must be started immediately, even before the diagnosis can be certain.

Immediate therapy should be directed to three areas: (1) respiratory support, (2) circulatory support, and (3) rapid anticoagulation. The administration of 100% oxygen may be necessary to increase the arterial P_{O_2} to a maximum. Isoproterenol should be given at a rate of 1 to 2 μg/min, and if systemic hypotension persists, norepinephrine may be used. Buffering agents such as sodium bicarbonate should be used to counteract acidosis. A central venous pressure catheter should be inserted, and 10,000 to 15,000 units of heparin should be given intravenously immediately. This prevents propagation of clot and possible bronchoconstriction caused by serotonin and other factors released by platelets. The central venous pressure may be used as a rough indicator of right ventricular heart failure. If it is normal in the presence of systemic hypotension, one should doubt the diagnosis of massive pulmonary embolus. If further cardiac support is necessary, a portable low-prime oxygenator may be used at the patient's bedside for partial bypass. Bypass can be instituted between the femoral artery and femoral vein, thus relieving venous congestion and improving the systemic and coronary circulation. Baseline blood studies are drawn, and the patient is taken immediately for pulmonary arteriogram. Should the patient respond to medical therapy long enough for this procedure, a decision must be made regarding operation. Interruption of the inferior vena cava must be performed, and if the patient does not respond to medical therapy, a pulmonary embolectomy is indicated. By the time a definite diagnosis is made, one has passed the steep, ascending curve of high mortality. Embolectomy should be reserved for those who fail to improve despite intensive conservative therapy.

In 1967 Cross and Mowlem[10] reported on the analysis of replies to questionnaires by 40 cardiovascular surgeons in the United States and Canada regarding their experience with massive pulmonary embolism; they found an overall operative mortality of 57% regardless of technique. In patients in whom no em-

bolus was found at operation, the mortality was 100%. This emphasizes the importance of an accurate early diagnosis prior to operative embolectomy.

Greenfield et al.[26] described transvenous removal of pulmonary emboli using a vacuum cup catheter technique. He initially demonstrated this in dogs and has now used this technique in three patients with acute massive pulmonary embolism. These patients had immediate hemodynamic improvement and subsequent complete recovery. This technique may prove to be a very important adjunct in the treatment of acute massive embolus.

CLINICAL PROBLEMS

Thromboembolic disease presents the physician with five clinical problems:

1. *The asymptomatic patient.* The major significance of this group is related to those who are in a high-risk category—older bedridden patients; those who are paralyzed; postoperative patients; patients with visceral malignancies, recent trauma, and a known history of thromboembolic disease; and patients with heart disease, particularly those in congestive failure. These patients should be treated with optimal prophylactic measures. Venous stasis should be avoided by active calf muscle exercises and leg elevation during bed rest. Prolonged sitting or standing should be avoided. Intraoperative intermittent leg compression, passive exercises, and galvanic stimulation of the calf muscles have been effective in reducing postoperative deep vein thrombosis. Small doses of subcutaneous heparin also have been effective and associated with minimal risk. The ultrasonic Doppler flow meter, impedance plethysmography, and ^{125}I fibrinogen scanning may be helpful in detecting early asymptomatic deep venous thrombosis. If these are unavailable, full anticoagulation therapy should be considered during the period of disability.

2. *Patients with symptoms referable to the leg but with no suggestive evidence of embolic disease.* They may present with edema of the ankle, swelling and induration of the calf muscles, and temperature elevation of the extremity. They may have calf pain and localized tenderness over any portion of the venous system. The Doppler technique or plethysmography may prove valuable in evaluating clinical thrombophlebitis if positive; however, for accurate diagnosis a phlebogram should be obtained. If these tests are positive, one should proceed to anticoagulation with heparin followed by the coumarins for a minimum of 6 weeks to 6 months. If the phlebogram is negative, one may assume that clinical findings are not secondary to thrombosis. Although fibrinolytic therapy may prove to be the treatment of choice, this is not established at present. If the viability of the leg is compromised by venous obstruction, thrombectomy is indicated.

3. *Patients with symptoms referable to the chest but whose legs test clinically negative.* Any patient with dyspnea, tachypnea, chest pain (particularly if pleuritic), hemoptysis, unexplained congestive heart failure, and chronic lung disease with unexplained deterioration should be evaluated for the possibility of pulmonary embolus. The initial workup should include a chest x-ray examination and lung scan, ECG, enzyme studies, and blood gas analysis. If the scan and chest x-ray film are negative, no therapy for embolism is needed. A positive perfusion scan with a negative chest x-ray film is an indication of pulmonary embolus and the patient should be treated. An arteriogram may be required for confirmation in cases in which the scan is positive with an associated infiltrate

on chest x-ray examination or if the scan is equivocal. Treatment with anticoagulants is the same as indicated in the previous category. If anticoagulants are contraindicated or fail to prevent emboli, venous interruption must be considered. Phlebograms should be performed to define the anatomic location and extension of the original thrombus.

4. *Patients with positive leg and chest findings.* In this situation, one would proceed in a similar manner to that just described.

5. *Patients with massive pulmonary embolus presenting catastrophically as acute cor pulmonale and respiratory distress.* In this situation the immediate aim of therapy is to support ventilation and circulation and produce immediate anticoagulation. Cardiac shock may be treated by supporting the circulation by partial bypass with a portable pump oxygenator. A definite diagnosis is made by pulmonary angiography. If the patient does not respond to medical therapy, a pulmonary embolectomy may be indicated. Vena caval interruption by the intravenous umbrella may be of particular benefit in these patients in order to prevent further embolization.

SUMMARY

Refinements in the technique of ascending phlebography, including fluoroscopy and image intensification, have made it a standard test in the diagnosis of deep venous thrombosis. Noninvasive techniques (the ^{125}I fibrinogen uptake test, ultrasound Doppler flow meter, and plethysmography) have been evaluated in comparison with this standard. These tests have better delineated the high incidence of asymptomatic deep venous thrombosis and are being used to define groups of patients who are at an increased risk of developing thrombosis. The ^{125}I fibrinogen uptake test has been very sensitive in detecting small thrombi in calf veins and has been used to monitor their propagation or lysis. This test is of particular value in prospective studies that are designed to evaluate methods of preventing thrombophlebitis. Further use of these techniques should vastly increase our knowledge of deep vein thrombosis and its therapy.

Pulmonary arteriography and lung scan have vastly increased our knowledge of pulmonary embolism. Patients who have unexplained cardiorespiratory difficulties should be suspected of having pulmonary embolism and should be evaluated initially with lung perfusion scans and chest x-ray examination in order to make a precise diagnosis. A high index of suspicion is necessary if patients presenting with minimal symptoms are to be identified and treated. Although anticoagulants are the mainstay in the therapy of thromboembolism, controlled studies are needed to evaluate fibrinolytic agents, since they may accelerate the resolution of both deep venous thrombosis and pulmonary emboli. New techniques of transvenous caval interruption and transvenous pulmonary embolectomy offer exciting new means of therapy that may replace operative procedures in the future.

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12

Management of esophageal atresia and tracheoesophageal fistula

ROWENA SPENCER

About November, 1696, I was sent for to an infant that could not swallow. The child seemed very desirous of food and took what was offered it with greediness, but when it went to swallow it, it was like to be choaked; and what should have gone down, returned by the mouth and nose, and it fell into a struggling convulsive sort of a fit upon it. It was very fleshy and large and was two days old when I was called to it, but the next day it died. . . .

. . . We cut open the thorax and taking out the gullet with the wind-pipe, lungs, etc., continued to the stomach. When we made a slit in the stomach and put a pipe in its upper orifice, and blowing, we found the wind had a vent, but not by the top of the gullet. Then we carefully slit up the back side of the gullet from the stomach upwards, and when we had gone a little above half way toward the pharynx we found it hollow no further. Then we began to slit it open from the pharynx downwards, and it was hollow till within an inch of the other slit, and in the imperforate part it was narrower than in the hollowed. This isthmus (as it were) did not seem ever to have been hollow, for in the bottom of the upper and the top of the lower cavity there was not the least print of any such thing, but the parts were as smooth as the bottom of an acorn cup.

Then searching which way the wind had passed we blew from the stomach upwards, we found an oval hole (half an inch long) on the fore side of the gullet opening into the Aspera Arteria, a little above its first division, just under the lower part of the isthmus above mentioned.*

Even though the literary style is different, this description of one of the earliest reported cases is clearly recognizable as the most common of the esophageal anomalies seen in the newborn period—atresia of the esophagus with a distal tracheoesophageal fistula. In the 272 years since this report was published a great many examples have been collected and classified, the embryology has been studied, and the surgical treatment has become so successful that a 90% survival rate can now be expected in a full-term infant with this condition.

*From Gibson, T.: The anatomy of humane bodies epitomized, ed. 6, London, 1703.

EMBRYOLOGY

The precise pathologic embryology responsible for the formation of atresia of the esophagus with or without tracheoesophageal fistula is unknown, since early stages of the malformation have not been identified in human (or other) embryos. A reasonable hypothesis can be formulated, however, by correlating the normal embryology with embryonic, fetal, and neonatal examples of the abnormality, with other anomalies in this region, and with analogous malformations in other regions, particularly the caudal end of the alimentary tract.

The earliest indication of the future respiratory tract can be identified in the human embryo when it is about 3 mm in size; a longitudinal groove develops on the ventral surface of the primitive foregut between the thyroid anlage and the hepatic diverticulum.[1] The most caudal extremity of this laryngotracheal groove deepens and enlarges to form a diverticulum that will later bifurcate and differentiate into the bronchi and lungs, but most of the length of the definitive trachea will be formed by septation of the original foregut.

In the 4 mm embryo, separation of the trachea from the esophagus is already underway. On the midlateral walls of the unpartitioned foregut, internal ridges arise, come into contact, and fuse in the midline to divide the original foregut coronally into a ventral trachea and a dorsal esophagus. This process starts caudally and progresses cranially to extend the tracheoesophageal septum up toward the level of the larynx.

Craniad progression of the tracheoesophageal septum and elongation of the trachea, esophagus, and remaining foregut occur simultaneously. By the time the embryo is 8 mm, the separation of the trachea from the esophagus is virtually complete.[18] Further embryonic development in this area is not pertinent to the present discussion, since completely developed esophageal atresia with tracheoesophageal fistula has been discovered in serially sectioned human embryos of 8.5 and 9 mm.[7, 21]

Simple arrest or minimal distortion of the normal embryologic development will result in several easily comprehensible anomalies that fall into two categories: (1) defective tracheoesophageal septation and (2) displacement of the tracheal or esophageal anlage.

Defective tracheoesophageal septation. Complete failure of division of the primitive foregut will result in the rare laryngotracheoesophageal cleft, the larynx and trachea remaining in continuity with the esophagus. Lesser degrees of this malformation will occur from arrest in the craniad progression of the septum, with the larynx and a variable portion of the trachea in communication with the upper esophagus.

Incomplete fusion of the lateral ridges that separate the tracheal and esophageal anlage will leave a window between the two viscera, producing the "H"-type tracheoesophageal fistula without esophageal atresia (Fig. 12-1, *E*).

Displacement of tracheal or esophageal anlage. Dorsal dislocation of a portion of the tracheal anlage will leave cartilaginous tracheal remnants in the wall of the esophagus[13] or will allow the formation of a lobule of pulmonary tissue that sometimes communicates with the lumen of the esophagus but always has a systemic blood supply (sequestration).

Displacement of esophageal epithelium into the respiratory tract also occurs.[20]

• • •

In view of the minimal deviation from the normal embryology necessary to produce the malformations just discussed, it would seem logical to assume that the resulting anomalies would occur rather commonly. However, they are quite rare, considerably more rare than esophageal atresia with or without tracheoesophageal fistula.

The remarkable uniformity in the gross pathology of esophageal atresias in the embryo, the fetus, and the newborn suggests a specific spacial or temporal aberration not easily explained by random inflammation, vascular accident, or pressure from adjacent viscera.[15] Zeit recognized this problem in 1912 when he wrote, "Arrested development of the lateral ridges which unite incompletely in the median line, as the ventral trachea and the dorsal esophageal tube is forming, would explain the fistula but not the atresia."[22] To explain the atresia another mechanism must be sought; here analogy with comparable anomalies in the caudal extremity of the primitive alimentary tract provides a lead.

The originally unpartitioned cloaca is divided into a dorsal rectum and a ventral urogenital sinus by a coronal septum, the urorectal fold. Just as in the formation of the tracheoesophageal septum, the septation proceeds from internally toward the outside at the same time that the midlateral walls fuse in the midline. As a matter of fact, division of both ends of the alimentary tract occurs at about the same time, and esophageal and anorectal atresia are often found in the same patient.

In the hindgut as in the foregut, anomalies of the dorsal anlage are more common than malformations of the ventral daughter chamber. Here, too, the disturbance in development that produces atresia of the dorsal alimentary tract is usually accompanied by a fistula to the ventral urogenital sinus. Also, the "H"-type side-to-side fistula is extremely rare, while the end-to-side fistula between the proximal (internal) bowel and the urogenital sinus is the rule. But in the caudal end of the gastrointestinal tract the mechanism responsible for the atresia is an abnormal extension of a normal embryologic process, i.e., excessive resorption of the tailgut that results in destruction of the dorsocaudal portion of the hindgut and produces absence or atresia of the rectum.[3]

Search for an analogous situation in the cranial extremity of the primitive alimentary tract reveals that the foregut is also the site of origin of a transient embryonic process, the neurenteric canal. The 1.5 mm human embryo is represented by a thin disc of cells lying between the amniotic cavity above and the yolk sac below.[9] In the middorsal line of the embryonic disc the notochord is proliferated cranially from Hensen's node. For a time the notochord forms a part of the dorsal wall of the yolk sac, and during this time there exists a communication from the lumen of the yolk sac to the amniotic cavity above. This communication, the neurenteric canal, extends from the yolk sac in the region of the esophageal anlage, through small temporary openings in the floor of the notochord, through the central canal of the notochord, and to the primitive pit just behind Hensen's node. Mesoderm from Hensen's node and from the primitive streak grows cranially, resulting in continuing enlargement of the head end of the embryo and in regression of Hensen's node and the primitive streak caudally. The neurenteric canal travels caudally with the primitive pit and then disintegrates as the last remnants of Hensen's node and the primitive streak disappear into the tailbud.

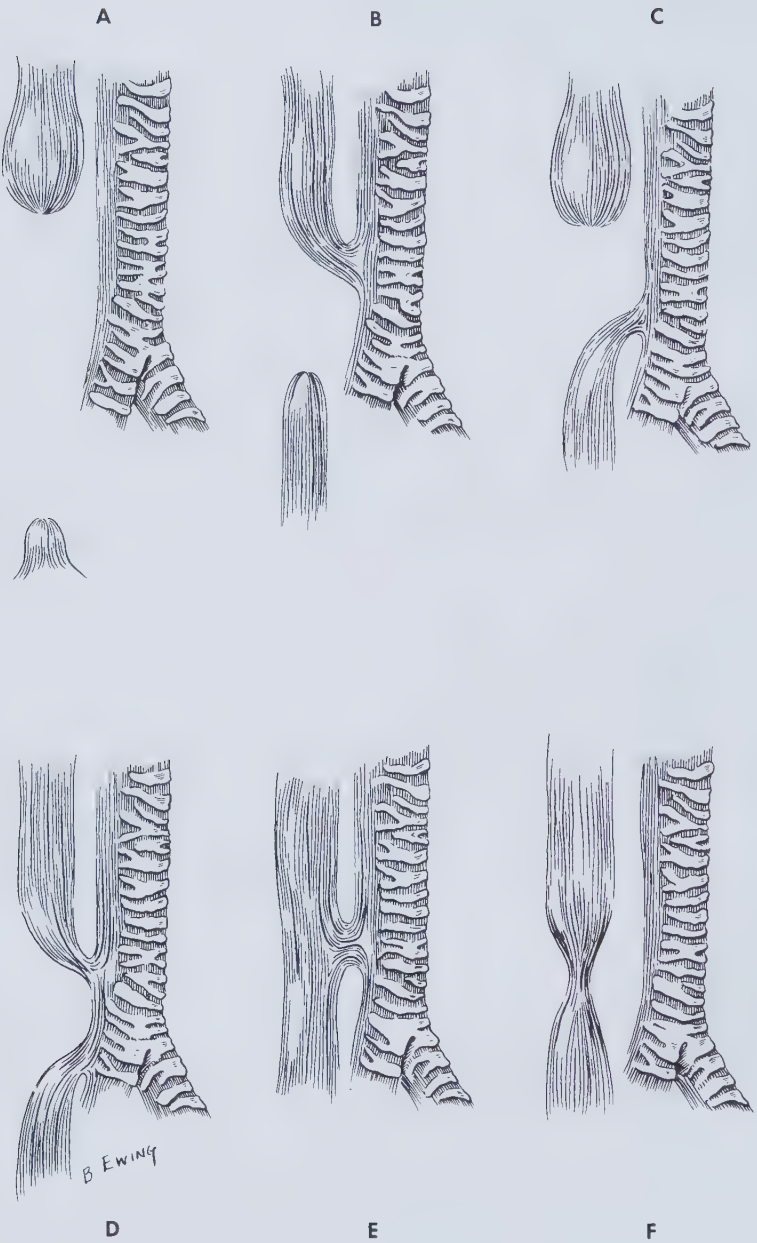

Fig. 12-1. Diagram of most common esophageal anomalies. **A**, Atresia without fistula. **B**, Atresia with proximal fistula. **C**, Atresia with distal fistula. **D**, Atresia with double fistula. **E**, Fistula without atresia. **F**, Stenosis without atresia or fistula.

Fig. 12-2. Diagram of rare types of esophageal anomalies. **A,** Atresia with distal fistula and continuity of muscularis (resembles congenital diaphragm with distal fistula). **B,** Same as **A,** but with extensive overlap of the upper and lower segments. **C,** Atresia with distal esophagobronchial fistula. **D,** Atresia with distal fistula and congenital diaphragm in distal esophagus. **E,** Atresia with double esophagobronchial fistula. **F,** Esophagobronchial fistula without atresia. **G,** Congenital diaphragm without fistula or atresia. **H,** Atresia of larynx, trachea (and attached bronchi) replacing midportion of esophagus.

Malformations resulting from defects of the neurenteric canal[14, 17] include (1) tubular duplication of the intestine, mediastinal enteric duplication cysts, and enteric cysts within the spinal canal; (2) anterior rachischisis, diastematomyelia, and combined anterior and posterior rachischisis with herniation of viscera posteriorly through the bifid vertebral column and spinal cord; and (3) enteric duplication associated with vertebral anomalies, esophageal adhesions to abnormal vertebrae, and persistent communication between the esophagus and the central canal of the spinal cord. To this multitude of rare anomalies of the neurenteric canal should be added esophageal atresia.[16] The only logical explanation for this malformation is damage to the primitive foregut from imperfect migration of the neurenteric canal or failure of the foregut endoderm to reform a continuous layer beneath the notochord in the region of the neurenteric canal. Since the endoderm of the esophageal anlage is only one cell thick and occupies less of the circumference of the foregut than does the tracheal anlage, a relatively small amount of damage will result in a relatively large defect in the definitive esophagus. Variations in the stage of development at which the defect occurs as well as the level and the extent of the damage will explain the variations in the anomalies seen clinically.

A long high defect will produce esophageal atresia without fistula (Fig. 12-1, *A*); a long low defect will cause atresia with a fistula from the upper esophagus to the trachea (Fig. 12-1, *B*). A short high defect will result in esophageal atresia with a blind upper segment and a fistula from the distal esophagus to the trachea (Fig. 12-1, *C*); a low short area of destruction will produce atresia with a fistula from both ends of the esophagus to the trachea (Fig. 12-1, *D*). (Destruction of an extremely short high segment will result in atresia of only the epithelial lining of the esophagus [Fig. 12-2, *A*], but with continuity of the muscular wall, which is formed later by accumulation of mesoderm around the endodermal tube.) As would be expected, the earlier and the more extensive the embryonic destruction, the higher the incidence of associated anomalies (Table 12-1).[10]

Table 12-1 *

	Incidence† (%)	Associated anomalies (%)
Atresia without fistula	8.0	58
Atresia with proximal fistula	0.9	55
Atresia with distal fistula	90.3	48
Atresia with double fistula	0.7	29
Fistula without atresia		27

*Data from Holder, T. M., et al.: Pediatrics 34:542, 1964.
†Figures recalculated from original publication to omit fistula without atresia since it has a different embryologic etiology.

DIAGNOSIS

The common types of esophageal atresia and/or fistula are illustrated in Fig. 12-1 and the more rare forms in Fig. 12-2. It will not always be possible to distinguish among these various kinds of anomalies before operation, but careful diagnostic studies will usually indicate the group into which they fall. With prior knowledge of the normal and abnormal embryology of these viscera and with thoughtfully planned dissection at operation, it should be possible to identify the type of malformation without serious difficulty.

Early manifestations of esophageal atresia include polyhydramnios (in the mother), difficulty in resuscitation at birth, excessive salivation, intermittent cyanosis, and aspiration of feedings. Once the suspicion of esophageal atresia has been aroused by these or other symptoms, there is no justification for delay in making a definitive diagnosis.

In the vast majority of patients, attempted intubation of the esophagus with a small red rubber catheter, size 8 or 10 French, will demonstrate the obstruction. The only anomalies that will escape detection by this means are the uncommon "H"-type fistula without atresia, the rare laryngotracheoesophageal cleft, and the extremely rare atresia of the trachea with the bronchi arising from the esophagus. (The patient with this latter anomaly will probably not survive long enough to have any diagnosis made.) In the case of a proximal fistula (Fig. 12-1, *B* and *D*), the catheter may pass into the trachea via the fistula and produce a paroxysm of coughing as the catheter meets with obstruction in the bronchus.

A small tape marker placed about 6 inches from the end of the catheter will indicate the level to which it should be advanced and prevent the error of inserting the same centimeter or two of catheter over and over again into the distensible and elastic upper esophageal pouch. Also, the distance to which it was advanced can be measured after removing the catheter. Since the catheter can coil in the esophagus instead of passing through it, it is important to ascertain that the catheter has actually reached the stomach. Aspiration of several milliliters of fluid will indicate that the stomach has been entered, but the blind pouch of the upper esophagus can also contain 1 or 2 ml of frothy mucus. The presence of the catheter in the stomach can be confirmed by injecting a small amount of air while auscultating the epigastrium.

Once the diagnosis of esophageal atresia has been made by esophageal intubation, the site and type of obstruction must be investigated by x-ray examination (Fig. 12-3). The type of contrast medium is not as important as the technique employed, provided the material used will not damage the tracheobronchial mucosa. A thin suspension of barium yields excellent results and will readily be removed by coughing if a small amount is spilled over into the trachea.

The size 8 or 10 French catheter is attached to a syringe and filled with contrast medium before it is reinserted into the esophagus. A measured 0.5 to 1 ml of contrast material is then injected and the catheter removed before the films are exposed. If it is not removed, the tip of the catheter may occlude the lumen of an esophageal stenosis (Fig. 12-1, *F*) and result in an erroneous diagnosis of a complete rather than a partial obstruction. An esophageal stenosis may also require operation but may not present the same urgency as an atresia. As soon as the films are made, the contrast material should be suctioned from the upper

Fig. 12-3. X-ray films of common esophageal anomalies. **A,** Atresia without fistula. **B,** Atresia with distal fistula. **C,** Atresia with double fistula. **D,** Fistula without atresia. **E,** Stenosis without atresia or fistula.

esophagus so it will not be regurgitated and aspirated into the trachea. More contrast material may be injected if it is necessary to repeat the study.

Injection of too much contrast medium may result in overflow into the trachea and, rarely, visualization of the distal esophagus and stomach via the fistula (Fig. 12-4). Aspiration of material spilled over into the trachea (Fig. 12-3, *B*) is to be differentiated from filling of the trachea through a proximal fistula (Fig. 12-5). In the former case the upper esophagus will remain full of contrast material; in the latter case the upper esophagus will usually not be visualized, since it will have emptied into the trachea via the fistula. The upper esophagus may also fail to appear on the film in the presence of a laryngotracheoesophageal cleft, which might previously have been suspected by the weak, soundless cry typical of the infant with this anomaly.

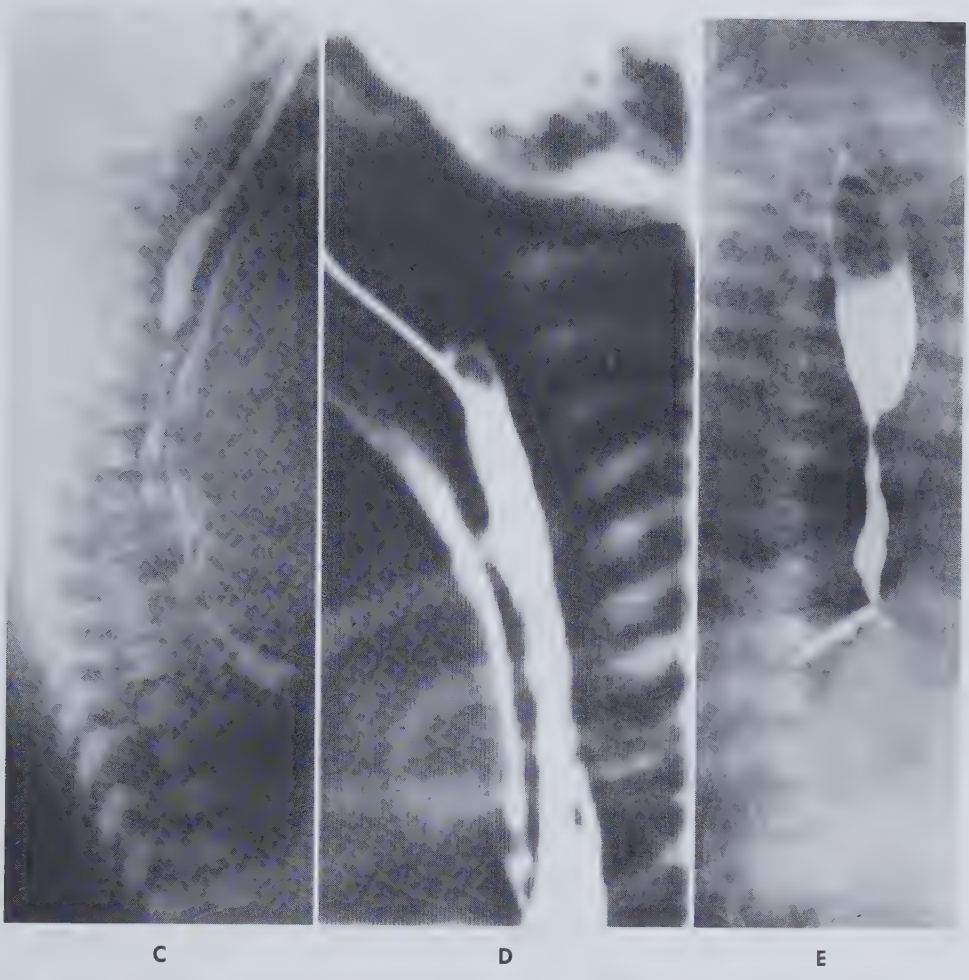

Fig. 12-3, cont'd. For legend see opposite page.

Careful placement of the catheter and slow injection of the contrast material under fluoroscopy or cinefluoroscopy will usually suffice to demonstrate the "H"-type fistula without atresia (Fig. 12-3, *D*), but occasionally other techniques will be required. Bronchoscopy and esophagoscopy are hazardous in the newborn period and usually fail to reveal the fistula. If the upper esophagus is occluded by the inflated balloon of a small Foley catheter and the contrast material injected slowly, the fistula will usually be visualized.[12] Occasionally it may be necessary to obstruct the lower end of the esophagus with a second Foley catheter or to place the patient in the prone position so the contrast material can enter the trachea by gravity. The level of the fistula must be identified with certainty, since the "H"-type fistula is often so high that it must be approached through a cervical incision or there may be more than one fistula present.

Fig. 12-4

Fig. 12-5

Fig. 12-4. Atresia with distal fistula. Barium was aspirated into trachea and fistula.
Fig. 12-5. Atresia with proximal fistula. Proximal esophagus has emptied into trachea.

The preoperative x-ray studies are not complete until the pattern of swallowed air in the stomach and intestine is demonstrated. It should be emphasized that even a very small amount of air in the stomach indicates a distal fistula and contraindicates simple feeding gastrostomy without thoracotomy, since regurgitation of feedings into the trachea through the distal esophagus can be expected in the presence of an intact fistula.

Absence of air below the diaphragm usually indicates absence of a communication between the distal esophagus and the trachea, but in a small, weak, or

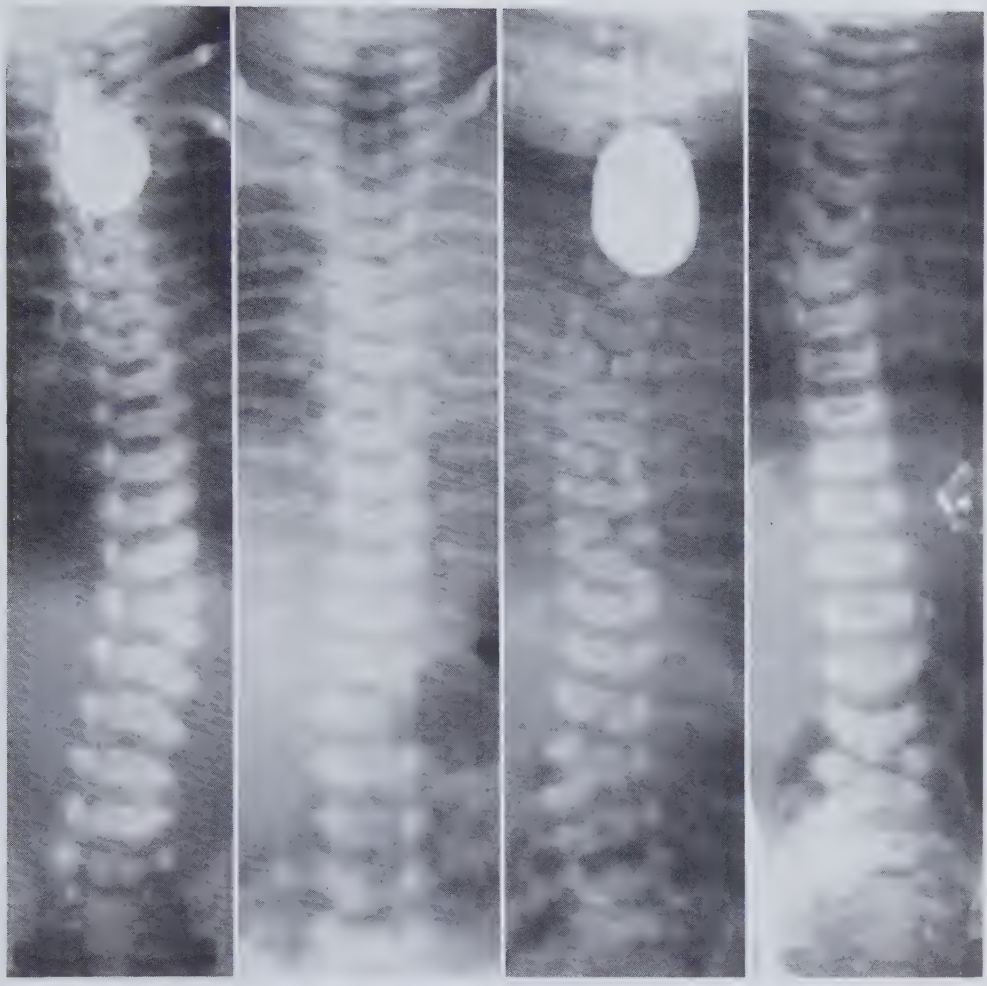

Fig. 12-6. Vertebral anomalies in four patients with esophageal atresia.

badly defective infant, air may not pass through a widely patent fistula.

Other abnormalities should be sought on the preoperative x-ray films. Vertebral malformations are commonly associated with esophageal atresia (Fig. 12-6). Over 10% of patients with esophageal atresia will have other gastrointestinal tract anomalies, the most common being duodenal and/or anorectal atresia. If there is a distal tracheoesophageal fistula, air in the stomach and duodenum may show the typical "double bubble" of duodenal atresia (Fig. 12-7) or the dilated loops proximal to a more distal obstruction. In the absence of air below the diaphragm, intestinal obstruction will be suspected when the abdomen is distended (Fig. 12-8) or when a firm rounded mass is palpable within the abdomen.

The films should be properly marked to avoid operating on the wrong side in the rare patient with situs inversus or dextrocardia. Preoperative aortography

Fig. 12-7. Esophageal and duodenal atresia with distal tracheoesophageal fistula.

through the umbilical artery should be performed whenever the heart is in an abnormal position and when plain x-ray films suggest any abnormality of the aorta.

PREOPERATIVE MANAGEMENT

There is no indication for rushing the usual patient with tracheoesophageal fistula to the operating room as a dire emergency, particularly in the middle of the night when the operating team is likely to be less than normally alert and the most skilled personnel not always available. On the contrary, most of these patients will benefit from a few hours of planned intensive treatment before being subjected to a major surgical procedure.

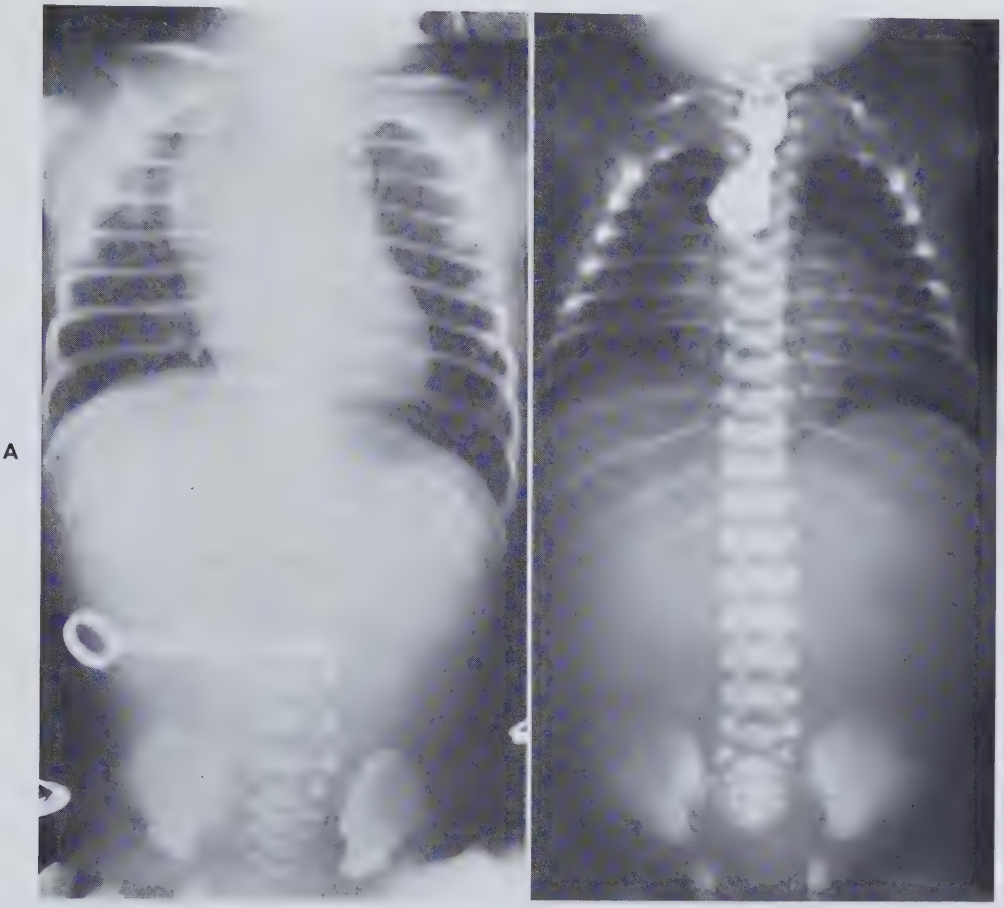

Fig. 12-8. Esophageal atresia without fistula. **A,** Without intestinal obstruction. **B,** With duodenal atresia causing abdominal distention.

The preoperative care of the patient with esophageal atresia is directed primarily toward prevention and/or treatment of pulmonary complications rather than correction of the fluid and electrolyte depletion that is usually present with obstruction lower in the alimentary tract. Infants are normally overhydrated at birth and can easily survive a day or two with no fluid intake at all. In addition, no electrolytes are required for the first 2 or 3 days after birth. Therefore the patient with esophageal atresia who will have lost no fluid other than saliva will require little preoperative fluid and no electrolytes if the diagnosis is made before 48 hr of age.

The newborn infant who has never assimilated formula has the low metabolic rate of the fetus and a correspondingly low fluid requirement. If intravenous fluids are indicated, approximately 10 ml of 5% glucose in water/pound of body weight can be given over a 2 or 3 hr period, followed by 5 to 10 ml/pound every 8 hr until operation. If blood gas studies indicate significant acidosis, 1 mEq of sodium bicarbonate/pound may be given in the initial loading fluid and each 8 hr until repeat blood pH studies are normal.

During this time the infant should be nursed in a warm incubator and his temperature maintained at a normal level. The relatively large body surface of the newborn results in rapid heat loss, particularly when the infant is exposed, unclothed, in air-conditioned radiology departments and operating rooms, and hypothermia not only raises the demand for oxygen but also increases metabolic acidosis.

Introduction of humidity in the incubator aids in liquefying pulmonary secretions. If there is associated difficulty in maintaining body temperature, a heated nebulizer is useful in providing both heat and moisture. Oxygen should be used only if there is cyanosis or respiratory distress and should be discontinued as soon as the infant is stable without it.

Broad-spectrum antibiotics are indicated and should be started before operation. It should be noted that tetracyclines and chloramphenicol are contraindicated in newborns and that procaine penicillin often causes sterile abscesses because it is not well absorbed. Ampicillin, 30 to 50 mg/pound daily, or aqueous penicillin, 50,000 to 100,000 units every 12 hr, and kanamycin, 7 mg/pound daily, are usually recommended.

Every newborn infant should be given vitamin K shortly after birth to pre-

Fig. 12-9. Pulmonary complications with esophageal atresia. **A,** Respiratory distress syndrome **B,** Bilateral pneumonitis. Both patients survived.

vent hemorrhagic disease of the newborn. This is specifically indicated in the infant scheduled for major surgery.

Care directed toward maintenance of the respiratory tract is probably the most important aspect of the preoperative treatment. The infant should be kept flat in the incubator. Elevating the head of the mattress may discourage reflux of gastric contents into the distal esophagus, but it will also encourage this and other fluid to pool in the dependent portions of the lung. If necessary a small sump may be placed in the upper esophagus, but secretions resulting from the irritation of an indwelling tube may offset the advantage of continuous removal of saliva. Frequent suctioning of the nasopharynx with a size 8 or 10 French catheter will usually remove the saliva and upper airway secretions and prevent aspiration of these fluids into the trachea.

It is important to have the infant turned frequently to encourage gravity drainage of all portions of the lungs. Particular attention should be given to maintaining or restoring normal aeration of the left lung, which will have to support oxygenation during operation. If significant pneumonitis or atelectasis is already present, formal postural drainage should be instituted with tapping over the affected areas of the lung. If there is respiratory distress syndrome of the newborn (Fig. 12-9, *A*) or persistent pneumonitis (Fig. 12-9, *B*), operation may be deferred 2 or 3 days or longer, if necessary.

If operation is to be delayed, gastrostomy done under local anesthesia will aid in preventing reflux of gastric juice through the patent tracheoesophageal fistula and in relieving the abdominal distention often present in the patient with respiratory distress. Routine gastrostomy in all patients will prevent aspiration of gastric contents during the period of preoperative preparation, but most healthy infants with tracheoesophageal fistulas will enjoy a completely uneventful hospitalization of approximately 1 week without ever having had a gastrostomy performed. However, the patient with a concomitant duodenal atresia or other intestinal obstruction will vomit large amounts of gastrointestinal secretions directly into the trachea and will obviously require immediate surgical attention, including gastrostomy.

The cardiovascular status should be carefully evaluated, since anomalies in this system frequently coexist with malformations of the esophagus. The most common cardiac anomaly is ventricular septal defect, which seldom causes any trouble in the newborn period and often closes spontaneously. If cardiac disease is so severe that failure seems imminent, it might be wise to undertake operation as soon as possible before decompensation occurs; otherwise control of the cardiac failure may delay operation beyond the optimal time.

THE OPERATION

During transport of the patient to the operating room and the operating table, every effort should be made to prevent loss of body heat. The extremities should be wrapped in cotton batting and the infant covered with warmed blankets before being removed from the incubator. A warm thermal mattress should await the patient on the operating table. Exposure of the unprotected body of the infant before and during preparation of the surgical field should be kept to a minimum, and the temperature should be monitored during operation with an indwelling rectal probe.

A satisfactory intravenous route must be established before operation is undertaken. A venous cut-down will be needed if a needle cannot be placed securely in a vein. Whole blood transfusion will not routinely be necessary, but if it is needed, approximately 10 ml of blood/pound of body weight will usually suffice. The same volume of either 5% glucose in water or a balanced electrolyte solution may be used to replace fluid lost during operation, but normal saline solution should not be given for replacement fluid or with the blood transfusion, since the tolerance of the immature neonatal kidney can easily be exceeded.

Most newborns can be intubated while awake, but the selection of this technique will be made by the anesthesiologist. It is quite important not to use excessive positive pressure in inflating the lungs before the fistula is divided, since the stomach distended via the fistula cannot be emptied with a nasogastric tube. If gastric distention does occur and is severe enough to interfere with respiratory exchange, percutaneous decompression of the stomach with a no. 20 or 21 needle may be necessary.

The surgeon may choose between the extrapleural approach, through the bed of the fourth rib, and the transpleural approach, through the right fourth or fifth interspace. The latter is more direct and requires less dissection to reach the mediastinum. The chest wall incision should be below the right nipple to avoid denervation of the serratus anterior and the latissimus dorsi with subsequent shoulder deformity and disability.[5]

The lung is allowed to collapse and is held medially and inferiorly with a small malleable retractor, taking care not to compress the trachea and right main stem bronchus and the heart and great vessels. The mediastinal viscera are most easily approached by dividing and ligating the azygos vein, but an unusually large azygos vein may represent the major venous return from the lower portion of the body (azygos continuation of the inferior vena cava). Under these circumstances the azygos vein should not be sacrificed; it may be mobilized by dividing the superior intercostal and, if necessary, other lower intercostal veins.

Gentle anterior traction on the proximal cut end of the azygos vein will expose the distal trachea and the most common location of tracheoesophageal fistula. Dissection in the areolar tissue posterior to the trachea will usually reveal the distal esophagus, but it can also be located by tracing the vagus nerve inferiorly. Mobilization of the distal esophagus should be no more extensive than necessary, and the branches of the vagus nerves and esophageal vessels should be preserved when possible. When the esophagus has been freed circumferentially, a divided, moistened thin rubber band may be passed around it (Fig. 12-10, *B*) and used to provide gentle traction to facilitate identification and dissection of the fistula.

The distal esophagus enters the posterior membranous portion of the trachea obliquely from below. The fistula should not be divided flush with the wall of the trachea. Subsequent closure of the defect would then result in stenosis of the trachea. Instead the fistula should be sutured at approximately the junction of the esophagus with the trachea and then the esophagus divided about 1 ml distal to the sutures (Fig. 12-10, *F*). A single row of simple or mattress sutures of 6-0 atraumatic silk will suffice. As each suture is placed and tied, that portion of the fistula is divided (Fig. 12-10, *C*) so that there is never a large air leak from the trachea. It is obvious that the fistula should be properly identified to

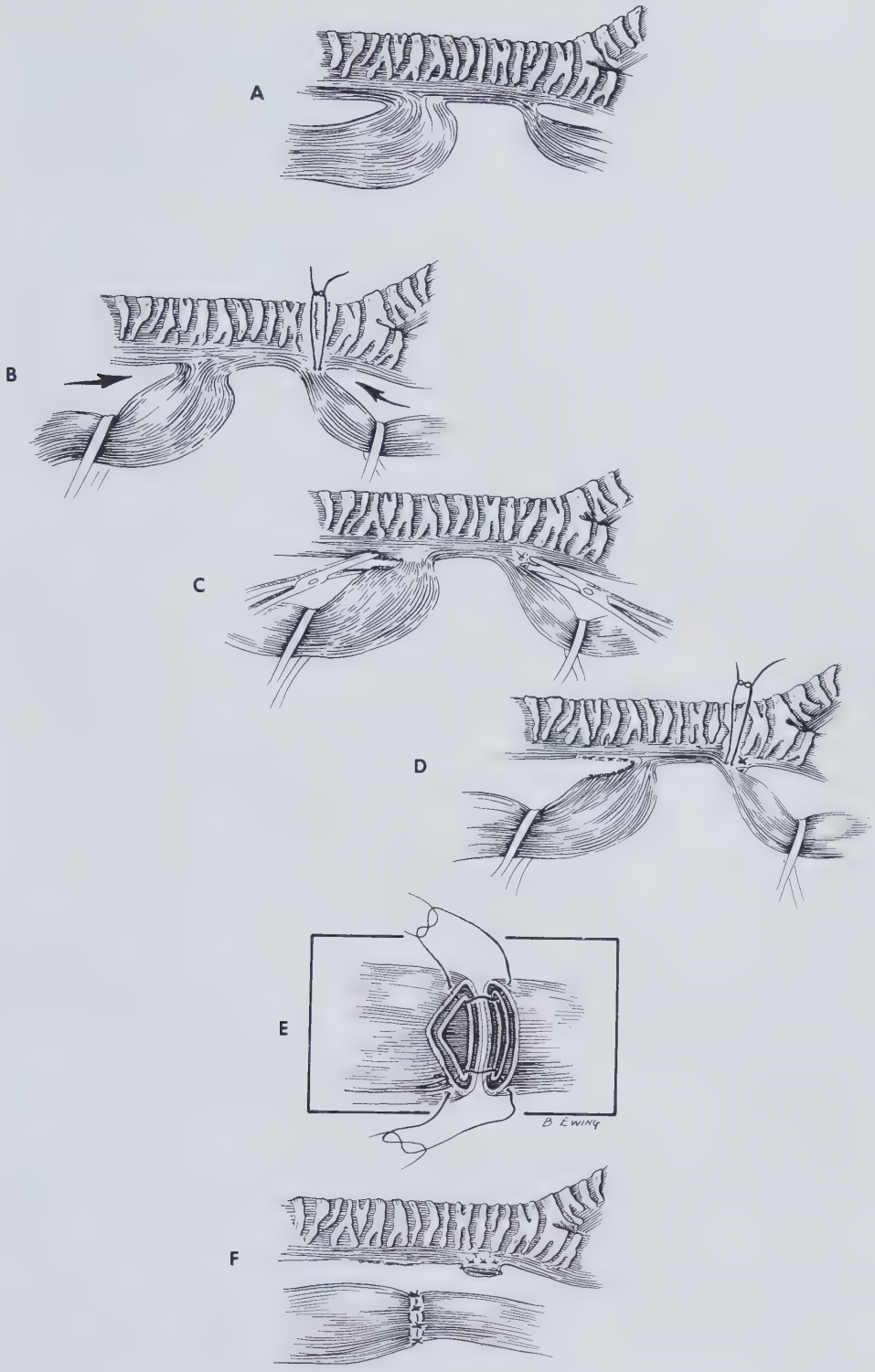

Fig. 12-10. Surgical technique used in dissection and anastomosis of esophageal atresia with distal fistula.

avoid dividing the right main stem bronchus by mistake. The cartilaginous rings in the bronchus should serve to differentiate it from the esophagus. When the fistula is completely divided, a size 8 or 10 French catheter is inserted through the esophagus and into the stomach to rule out the presence of an obstruction in the distal esophagus. Aspiration of gastric contents through this catheter may facilitate respiratory excursions. If bile-stained material is obtained, intestinal obstruction should be suspected.

Normally the esophagus distal to an atresia is considerably smaller than the dilated and hypertrophied proximal segment. A large dilated distal esophagus will indicate the possibility of intestinal obstruction, usually duodenal atresia, that might have been suspected preoperatively if the patient coughed up bile-stained secretions and if the x-ray films showed an abnormal intestinal gas pattern. In the patient without distal tracheoesophageal fistula (Fig. 12-1, *A* and *B*) a distended distal esophagus is an indication for laparotomy.

The proximal esophagus can usually be readily identified in the apex of the pleural space. If necessary, the anesthesiologist can exert gentle pressure on the blind pouch with a catheter passed through the nose or mouth.

The most distal portion of the blind pouch is always densely adherent to the posterior membranous wall of the trachea (Fig. 12-10, *C*). To avoid entering the trachea at this point, it may be advisable to dissect the esophagus from the trachea proximal to the area of scarring and then work distally in the angle between the two viscera. A small opening in the trachea can be safely closed with oiled 6-0 silk sutures, but every effort should be made to avoid incorporating so much tissue in the sutures that tracheal stenosis results.

The proximal portion of the esophagus can be mobilized as extensively as necessary. Its thick hypertrophied walls will have adequate intramural blood supply. During mobilization, dissection should be carried out quite close to the wall of the esophagus to avoid damage to the recurrent laryngeal nerves. During this dissection a retroesophageal right subclavian artery may be encountered, running from below and medially across the apex of the chest laterally and superiorly. It may be divided if necessary, but it is not likely to cause any obstruction postoperatively. Of more concern will be anomalies of the aorta. A right aortic arch will create serious problems in dissection and anastomosis of the esophagus. A right descending aorta will usually not cause difficulty at operation, but both of these anomalies will indicate other more serious cardiovascular malformations.

If a primary anastomosis can be accomplished, a small incision is made right in the bottom of the proximal pouch and the two ends of the esophagus approximated. The specific type of anastomosis is not as important as the technique used in handling the tissue. The incidence of postoperative stricture will vary directly with the number of times the cut edges of the esophagus are grasped with forceps and other instruments. When possible the lumen should be exposed with a blunt nerve hook or the (closed) end of a curved mosquito hemostat, grasping with forceps only the areolar tissue around the esophagus.

The advantages and disadvantages of the various types of anastomosis will have to be weighed by the individual surgeon. Suffice it to say that the more the sutures and the layers of sutures used, the higher the incidence of postoperative stricture, and the fewer the sutures and the layers of sutures used,

the greater the number of leaks at the suture line.[10] A single layer of simple sutures of 6-0 silk, 1 or 2 mm apart and 1 or 2 mm from the cut edge of the esophagus, carefully incorporating the mucosa in every suture (Fig. 12-10, *E*), will yield a satisfactory result in the vast majority of patients. Usually only seven or eight sutures are required. If more are used, the surgical trauma and the interference with blood supply will result in a high incidence of both leaks and strictures.

In the usual case, tension on the suture line can be avoided by adequate mobilization of the esophagus, primarily of the upper segment but also of the lower segment if necessary. Moderate tension will result in a larger number of postoperative complications (leak and stricture), but the risk may be acceptable in view of the undesirability of subsequent colon interposition or other esophageal replacement. If tension is excessive, however, attempts at direct anastomosis should be abandoned and cervical esophagostomy and gastrostomy planned. If possible, the decision concerning the feasibility of primary anastomosis should be made before the proximal esophagus is opened. Once it is entered, cervical esophagostomy must be done at the same sitting, but if it remains intact, esophagostomy can safely be delayed 48 to 72 hr. When the infant has recovered from the stress of the thoracotomy, both esophagostomy and gastrostomy can safely be done under local anesthesia.

Even though primary anastomosis is not contemplated, the proximal end of the esophagus should be completely mobilized via the thoracotomy to facilitate subsequent cervical esophagostomy, particularly if local anesthesia is to be used for the esophagostomy.

As the esophageal anastomosis is being completed, the anesthesiologist is asked to insert a size 8 or 10 French catheter through the nasopharynx and, as he removes it, to measure the distance from the external nares to the anastomosis. This will serve as a guide to the distance to which the nasopharyngeal suction catheter can safely be inserted postoperatively. The mediastinal pleura is closed only over the anastomosis, so that postoperative leakage, if it occurs, will drain into the pleural space instead of being confined to the mediastinum. The chest should be aspirated of air while the incision is being closed, but it is not necessary to leave a drainage tube in the chest. It can be inserted later if complications indicate.

Alternative procedures are available for the infant who is unable to tolerate thoracotomy and primary repair, e.g., the infant who is premature, weak, or septic or has multiple anomalies. These procedures include (1) gastrostomy and extrapleural ligation of the fistula and (2) gastric division and "double-barrel" gastrostomy. In both of these instances the proximal esophagus is drained with either a nasopharyngeal sump or a temporary lateral pharyngostomy until definitive repair of the fistula and the atresia can be accomplished. Also, the patient with esophageal atresia without fistula usually has absence of so large a portion of the thoracic esophagus that primary repair is not possible. In this latter patient it may be possible to stretch the upper esophageal segment with mercury bougies and other devices while the infant is nourished via a gastrostomy. In all three of these multistage procedures the infant must remain in the hospital for several weeks before definitive repair can be undertaken, and the incidence of fatal gram-negative infection in the tracheo-bronchial tree or in the subsequent

operative area is prohibitively high. Under most circumstances, immediate surgical repair of the atresia and the fistula or cervical esophagostomy and gastrostomy will yield the greatest number of survivors.

High mortality and morbidity do not attend gastrostomy and cervical esophagostomy, since free drainage of saliva from the stoma will obviate the need for repeated suctioning (and contamination and trauma) of the upper airway. The patient can be sent home to grow and develop outside the hospital environment, and esophageal replacement can be undertaken when the child reaches an appropriate age, usually age 1 to 2 years.

In the operative approach to cervical esophagostomy a 1.5 to 2 cm incision is made under local anesthesia just above the left clavicle, behind the sternocleidomastoid muscle or between its two heads. If the esophagus has been mobilized at prior thoracotomy, as it should have been, a sucking wound of the chest will be created when the esophagus is brought out of the mediastinum and into the cervical incision. Pneumothorax can be prevented if the anesthesiologist will maintain positive pressure with a close-fitting face mask during this portion of the procedure. It is imperative that the stoma be created at the most distal portion of the upper esophageal pouch, suturing esophagus to both subcutaneous tissue and to skin. Except as a temporary measure as noted previously, lateral pharyngotomy is specifically contraindicated, since the blind pouch distal to the stoma will accumulate saliva that will then be aspirated into the trachea.

The incision for gastrostomy in a newborn should be made transversely over the lateral half of the left rectus muscle, approximately halfway between the xiphoid and the umbilicus. This also can be done with local anesthesia. The postnatal descent of the costal margin will create problems if the gastrostomy stoma is too close to the rib margin in the neonatal period. If the incision is no more than 2 or 2.5 cm long, troublesome intraoperative evisceration of bowel will not occur. The gastrostomy should be midway between the cardia and the pylorus and midway between the greater and lesser curvatures. Placement of the tube too close to the pylorus may mechanically obstruct the gastric outlet and also facilitate later prolapse of the tube into the duodenum with resulting "unexplained" vomiting and gastric distention. The anterior gastric wall is usually large enough to accommodate two purse-string sutures, the second of which is used to anchor the stomach to the parietal peritoneum. A latex Pezzer catheter, with the distal half of the "button" cut off, is used, since it is not likely to be accidentally displaced in the immediate postoperative period. A size 16 or 18 French catheter is appropriate for most newborns, but in the patient who has esophageal atresia without fistula, it may be impossible to use anything larger than an 8 or 10.

Under most circumstances it is probably advisable to explore the chest in patients suspected of having atresia without fistula to confirm the absence of a tracheoesophageal fistula. Rarely a patient with a patent distal esophagus in wide communication with the trachea will fail to have air in the stomach, resulting in an erroneous diagnosis of absence of a fistula. Also, occasionally a primary esophageal anastomosis can be performed in the patient who has atresia without fistula.

Should it be elected to perform gastrostomy without prior exploration of the chest, the absence of a fistula must be confirmed by evaluating the status of the

stomach. A suspicion of even the smallest amount of air in the stomach before or during operation warrants the most careful attention, since gastrostomy feedings in the presence of an intact fistula will permit vomiting directly into the trachea—a usually fatal occurrence. In the absence of a fistula the gastric wall will be thicker than normal and the lumen only slightly larger than that of the normal small bowel. Gastrostomy with even the smallest catheter will be extremely difficult. Usually only one purse-string suture can be used, and the postoperative feedings will begin with only 2 or 3 ml of fluid.

On the other hand, if the configuration and caliber of the stomach and the thickness of the gastric wall seem normal, it is probable that a fistula does exist. If the stomach is round and firm and fully distended with fluid but not air, esophageal atresia without fistula coexists with intestinal atresia, usually duodenal. Exploration of the remainder of the abdomen will then be mandatory.

In most patients, primary repair of both esophageal and duodenal atresia at one sitting is contraindicated, but if the infant is full term and in good condition and if both procedures can be accomplished in only 2 or 2½ hr, this may be the preferable course. Otherwise a decision must be made as to which atresia to repair first.

In contradistinction to the patient with only esophageal atresia, the infant with both esophageal and duodenal atresia must have a gastrostomy to decompress the hypertrophied upper gastrointestinal tract, which is notoriously slow to exhibit effective peristalsis after operation. Obviously prolonged nasogastric intubation for this purpose would interefere with the healing of the esophageal anastomosis. If repair of the duodenal atresia and gastrostomy are performed first, the anchoring of the gastric wall incident to the gastrostomy may prevent subsequent mobilization of the stomach if this should be necessary to accomplish a primary anastomosis in a short esophagus.

It is usually preferable to repair the esophageal anomaly first to prevent the aspiration of vomitus that must exit via the trachea. A size 5 French plastic feeding tube slipped through the anastomosis at operation will serve as adequate short-term decompression of the stomach without obstructing the passage of saliva through the esophagus and without interfering with the circulation in the area of the anastomosis. Within 36 to 48 hr the abdominal procedure can be accomplished under local anesthesia and the esophageal tube removed when the gastrostomy is established.

Repair of the "H"-type tracheoesophageal fistula without atresia is generally not difficult if two facts are kept in mind: (1) the fistula may be at or above the level of the clavicle, where it must be approached through a cervical incision, and (2) there may be more than one fistula present. This "side-to-side" fistula is closed as described above, i.e., with a vertical row of 6-0 silk sutures placed at the junction of the trachea and the esophagus, dividing the esophagus about 1 ml distal to the sutures and thus leaving a small portion of esophageal tissue on the posterior wall of the trachea. The esophagus is then closed transversely with a single layer of simple sutures.

POSTOPERATIVE CARE

The problems encountered in the immediate postoperative period are (1) establishment of adequate respiratory exchange, (2) maintenance of body

temperature, (3) confirmation of complete expansion of the right lung, and (4) prevention of pulmonary complications.

Blood gas studies will show that most infants are acidotic after an operation of this magnitude. Despite all efforts, body temperature usually drops 2° or 3° and respiration is often depressed when the infant is allowed to resume spontaneous respiration after the pleura is closed. The resulting combination of metabolic and respiratory acidosis may be suspected in an infant who is pale or faintly cyanotic, quiet and inactive, and has a poor cry even when stimulated. A dramatic improvement may follow a single dose of sodium bicarbonate, about 1 ml/pound of body weight, injected intravenously over a 10 min period. More rapid injection may result in cerebral hemorrhage from the rapid shrinkage of the brain associated with abrupt hypernatremia. Repeat blood gas studies will determine the need for additional bicarbonate.

The infant should be transported to the recovery area in a preheated incubator flushed with oxygen and the postsurgical chest x-ray film taken through the top of the closed incubator. If this film shows no significant abnormality, and no postoperative complications develop, the next x-ray film will be taken approximately a week later, the day before the child is discharged from the hospital.

The most important continuing problem in the postoperative period is prevention of pulmonary complications. Newborns normally have inactive gag and cough reflexes, and after operation depression of these reflexes may lead to aspiration of saliva and mucus and result in pneumonitis and atelectasis. The prognosis is good in the infant who coughs during suctioning and who is able to maintain a clear airway by swallowing and spontaneous coughing after operation.

Using as a guide the catheter with which the anesthesiologist measured the distance from the external nares to the anastomosis, a size 8 or 10 French catheter is prepared for nasopharyngeal suctioning. A tape marker is placed at a distance that will keep the tip of the catheter at least 1 cm above the suture line. This catheter, never inserted past the marker, is used to suction the nasopharynx at least hourly or more often as indicated by the volume of secretions aspirated. Most atropine derivatives used as preoperative drying agents will reduce secretions for nearly 24 hr, at which time there is a significant increase in the volume of aspirate from the upper airway.

Antibiotics are continued after operation and intravenous fluids resumed at the rate of 15 to 20 ml/pound daily. This fluid may be increased 5 to 10 ml/pound every day until a maximum of 35 to 40 ml/pound daily is reached. After the third day of life, a balanced electrolyte solution is substituted for the glucose solution in order to provide 0.75 to 1 mEq/pound daily of both sodium and potassium.

If the chest is clear and the infant able to swallow saliva adequately, oral feedings with a medicine dropper are started about 48 hr after operation, beginning with 2 to 3 ml of sugar water every 2 hr. The nurse is instructed to fill only the tapered end of the dropper to prevent the infant from sucking too large an amount from the dropper at one time. Every 12 hr the volume of the feedings is increased, and after 24 hr, formula is given. When the volume reaches half an ounce, feedings may be given with a new hard nipple. If all

goes well, the infant should be taking as much formula as he likes within a week after operation, at which time he is ready to go home.

The most dreaded—and most life-threatening—complication is a leak at the anastomosis. This will be suspected when the respiratory rate suddenly increases, usually 3 to 5 days after operation. Auscultation will reveal an absence of vesicular breath sounds on the right, and chest x-ray films will show a pneumothorax on that side (Fig. 12-11). If the diagnosis is made promptly, there will be little fluid in the chest.

Treatment of a leaking anastomosis consists of immediate tube thoracostomy with a size 16 or 18 French catheter that is attached to controlled, continuous water-seal suction. Since oral intake is now impossible, gastrostomy must be done as soon as the general condition of the infant has stabilized. In an occasional patient, reflux of gastrostomy feedings through the leak will indicate jejunal feeding via a small tube threaded through the pylorus and duodenum or formal parenteral hyperalimentation. Cervical esophagostomy and thoracotomy

Fig. 12-11. Pneumothorax caused by a leak in an esophageal anastomosis.

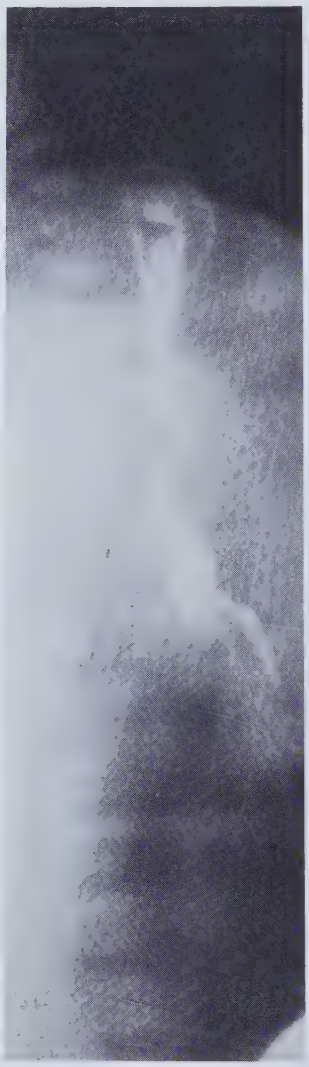

Fig. 12-12. Recurrent tracheoesophageal fistula.

to close the distal esophagus are usually not necessary, since the entire anastomosis is rarely disrupted and a small leak can be expected to close if the pleural space is adequately drained. The incidence of stricture is very high after anastomotic leak.

A small anastomotic leak with rupture of the resulting localized abscess through the tracheal suture line probably accounts for a recurrent tracheoesophageal fistula (Fig. 12-12). This will be suspected in the infant who has difficulty managing oral feedings and has recurrent pneumonitis and atelectasis. Abnormal abdominal distention may accompany the respiratory problems. The diagnosis can usually be confirmed by routine barium swallow, but occasionally this acquired "H"-type fistula must be diagnosed with the technique recommended

Fig. 12-13. Postoperative stricture. **A,** Mild. **B,** Severe.

for the congenital fistula without atresia. However, contrast material should be administered with caution, since stricture almost invariably accompanies recurrent fistula. Treatment consists of repeating the initial surgical procedure—dividing and closing the fistula and, usually, resecting the stricture and reanastomosing the esophagus.

The dysphagia of postoperative stricture without recurrent fistula (Fig. 12-13) usually begins after the child has been discharged from the hospital, most often a few weeks to a few months after operation. The gradual contracture of the suture line often allows the infant to nurse slowly rather than aspirate the formula, but the mother should be instructed to report either noisy respiration or respiratory distress associated with feedings. A stricture that responds to a

few dilatations, perhaps with injection of triamcinolone, needs no other treatment but reoperation is preferable to prolonged, repeated dilatation. The stricture can usually be resected and the ends of the esophagus reapproximated, but if the original anastomosis was made under tension, colon interposition will probably be required.

Oral intake should be encouraged in the child with a cervical esophagostomy and a gastrostomy so he will learn to taste and enjoy the food he will subsequently be fed. However, it is a rare infant who will continue to eat food that does not comfort his stomach and allay his hunger, and it often requires several weeks of slow and painstaking effort to teach the child to eat again after successful esophageal replacement.

FOLLOW-UP

Neither an esophagram nor dilatations will be needed in the patient who continues to swallow normally after discharge from the hospital. Instead, the esophagus may be calibrated periodically beginning 2 to 3 weeks after operation when a size 16 catheter should pass readily into the stomach of a full-term infant. The esophagus should tolerate a size 20 catheter by 3 months of age and a size 30 by 6 months of age. If the suture line cannot be identified with these catheters, no dilatation or x-ray studies should be done.

After discharge from the hospital, the mother is instructed to allow the infant to nurse as rapidly as he wishes, as long as there is no significant dysphagia or dyspnea. Solid food may be offered at the usual age but must be given with extreme caution. A hungry infant trying to force a large amount of thick food through a narrowed esophagus may suffer fatal aspiration. The first food, usually cereal, is made very "soupy" with milk and the consistency gradually increased to normal if the infant has no dysphagia. All new foods are introduced in the same manner, particularly if the consistency is greater than that of the previous diet, but the usual pureed "baby food" will rarely cause difficulty if cereal is handled well.

Cookies and crackers will constitute the next hurdle. Later rice, soft bread, and unchewed portions of meat may hang up at the suture line. Essence of caroid, small sips at first and increasing to a teaspoonful an hour, will usually soften such an impacted bolus so that it can pass into the stomach without requiring extraction via esophagoscopy. However, coins and marbles that fail to pass the scar at the suture line cannot be expected to respond to this medication and will require early instrumentation.

The mother should be instructed to allow the child to eat normally if he can. She should not offer only very small morsels of food and require that they be chewed especially well. The most efficient esophageal dilator is a hungry youngster with a large mouthful of unchewed food—the normal diet of small children. Obviously, however, the eating habits must be supervised in a patient with a stricture.

In contrast to the patient with a postoperative stenosis, from whose diet all solid food may be removed, the patient with neuromuscular dysfunction has most difficulty with water and milk and benefits greatly from thickened feedings—ordinary formula to which cereal is added. The existence of this dysfunction should not be unexpected, since a segment of esophagus is embryologically

lacking and the adjacent esophagus is mobilized to facilitate an anastomosis. It is surprising only that it does not occur more often, since cinefluoroscopic studies show that there is always a demonstrable abnormality of peristalsis in the esophagus after repair of an esophageal atresia.

RESULTS

The yardstick against which the results of surgical treatment of esophageal anomalies are measured is the report of Holder et al.[10] of a survey of 1058 patients treated between 1958 and 1963 by the members of the Surgical Section of the American Academy of Pediatrics. Mortality in this collected series was 39%, with a 17% incidence of leak at the anastomosis (61% of which were fatal), and a 40% incidence of stricture. Other recent series report mortality rates of 26% to 38%.[2, 4, 8]

From July 1959 to July 1973 I treated a total of 59 patients with these malformations both in private hospitals and in the Charity Hospital of Louisiana at New Orleans, with a 19% mortality, a 15% incidence of leak (with a mortality of 33%), and a 22% incidence of stricture (Table 12-2). Transpleural approach was used on all patients, and all but three had a single-layer anastomosis, the other three having a Haight anastomosis (approximation of the full thickness of the lower esophagus to only the mucosa of the upper segment, with the muscularis of the upper segment then pulled down over this layer of sutures and approximated to the external surface of the muscularis of the distal esophagus). All three of these patients developed a stricture (Fig. 12-13); one also

Table 12-2. Results of treatment

	4 lb or less	4 lb, 1 oz, to 5 lb	5 lb, 1 oz, to 6 lb	6 lb or over*	Total
Number of patients	10	9	9	31	59
Deaths	5		5	1	11
Inevitable	2		3	1	6
Leak	2			3	5
Fatal	2			1	3
Leak and stricture	1	2		1†	4
Stricture	2	1†		6†	9
Other major anomalies	7	1	7	5	20
Mortality					
Present series (1959-1973)	50%	0	55%	3%	19%
Holder et al.,[10] 1058 patients (1958-1963)	73%	53%	65%	12%	39%
Daum et al.,[2] 47 patients (1959-1966)					38%
Haight,[8] 100 patients (1956-1968)					26%
Ferguson,[4] 69 patients (1954-1970)					29%

*This category includes 12 patients listed as full term without a specific weight given.
†Each of these categories includes one patient with a Haight anastomosis.

had a leak at the anastomosis and a recurrent tracheoesophageal fistula (Fig. 12-13).

Survivors in this present series include three infants with both esophageal and duodenal atresia, all of whom had other anomalies and two of whom weighed less than 4 pounds. At least 10 patients had complete or partial expression of the VACTERL syndrome (*v*ertebral, *a*nal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal, and *l*imb deformities).

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13

Arterial reconstruction below popliteal artery

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The natural evolution of arterial reconstructive procedures has been one of successful repair of progressively smaller and smaller vessels. As techniques for vascular surgery have improved and surgeons have become more familiar with the handling of smaller vessels, successful treatment of increasingly distal arterial occlusion has become possible. Thus the early operations on the thoracic and abdominal aorta have been followed in turn by the treatment of lesions of the iliac, femoral, and popliteal arteries. In 1949 Kunlin[13] first described femoral popliteal bypass grafting using a reversed saphenous vein. In the 1950's and 1960's, as synthetic materials became more popular as grafting agents for occlusions below the inguinal ligament, the popliteal artery was the distal limit for arterial reconstructive procedures. However, as refinements in the techniques of suturing blood vessels have been made and as the saphenous vein has supplanted the synthetic graft, the success rate in bypass grafting smaller vessels has improved.

Direct arterial surgery beyond the popliteal artery was doomed to failure in the era of the synthetic graft because of the small size of the vessels involved and the poor "run off" from this arterial bed. As experience was gained with the use of autogenous vein bypass procedures, however, it became obvious that poor "run off" per se was not a limiting factor for successful grafts. Implantation of the distal end of an autogenous saphenous vein into an isolated popliteal segment (with, in effect, no "run off") was shown to be attended by a high success rate when the procedure was properly performed.[16] Refinements in the techniques of suturing small blood vessels have resulted in high patency rates for anastomoses of vessels 1 to 2 mm in diameter. Obviously careful, meticulous technique, small instruments, fine suture materials, and magnification aids are essential to achieve these results. Utilization of the techniques for small vessel anastomoses and a better understanding of the principles of grafting in relation

to inflow and outflow requirements have permitted successful grafting to vessels below the popliteal trifurcation. Successful saphenous vein bypass grafts to the anterior tibial, posterior tibial, and peroneal arteries have been reported by many groups in the past few years.

The initial report of McCaughan[15] in 1961 of successful arterial grafts below the popliteal trifurcation opened the way for increasing usage of infrapopliteal arteries in arterial grafting. The application of these extended grafts for grafting procedures below the popliteal artery has resulted in many examples of limb salvage in patients otherwise faced with amputation of their limbs.

Concomitant with the improvement in direct arterial surgical techniques has been an improvement in rehabilitative methods, including improved physical therapy and improved prosthetic devices, especially the use of immediate post-surgical prostheses. These methods have allowed earlier and better ambulation of patients with arterial occlusive disease who require amputation. Therefore the evaluation of infrapopliteal grafting procedures must be made within the framework of the improved outlook for rehabilitation of patients requiring amputation.

CLINICAL MATERIAL

The characteristics of the patients requiring infrapopliteal grafting have been somewhat different than those of the routine patient requiring femoral popliteal bypass grafting. Whereas progressive or incapacitating claudication is frequently an indication for the standard femoral popliteal grafting, almost all patients requiring grafting below the popliteal artery have limb-threatening conditions, i.e., minor degrees of gangrene, nonhealing ulcers, and/or rest pain. Analysis of 36 patients at The Jewish Hospital of St. Louis who were undergoing infrapopliteal bypass procedures indicated that they are an elderly group with an average age of 74 years. Severe generalized arteriosclerosis is frequent, with 66% of the patients undergoing infrapopliteal grafting having had either a previous myocardial infarction or a cerebral vascular accident. There is an extremely high incidence of diabetes mellitus in this group, with 70% of the patients having proved diabetes. Thus the surgeon is often confronted with the dilemma of a seriously ill elderly patient threatened with loss of a limb, in whom a difficult distal grafting procedure is required.

SUCCESS RATE

I have been able to find a total of 484 individual patients reported in the English literature who have been treated for arterial occlusive disease by vein grafting below the popliteal trifurcation.* In addition, 36 procedures of revascularization below the popliteal artery have been performed at The Jewish Hospital of St. Louis.[23, 24] Thirty of these 36 patients, or 83% of the patients from The Jewish Hospital, and 384 of 484, or 79.3% of the patients recorded in the English literature, have had successful early patency of the vein grafts to the infrapopliteal arteries. Thus early patency rates for surgery of infrapopliteal occlusions is as high or higher than many series of routine femoral popliteal bypass grafts. Undoubtedly this is a highly acceptable percentage rate for

*See references 1 to 12, 14, 15, 17, and 19 to 22.

early patency when considering the almost certainty of amputation in these patients if no direct arterial surgical procedure is performed. The seeming paradox of the high patency rate is made understandable, however, when one realizes that the patients undergoing infrapopliteal bypass grafting are a highly selected group as opposed to the more routine "all comers" femoral popliteal grafting patients. Also, as had been pointed out by Reichle and Tyson,[21] minimal arteriosclerotic change is most frequently noted in the tibial arteries usually selected for infrapopliteal grafting. The arteries distal to the popliteal occlusion are often as soft and as free from arteriosclerotic plaques as the autogenous saphenous vein being used for the bypass. However, often when the popliteal artery is used for grafting it is hard or calcified or extensively diseased, causing the anastomosis to be technically difficult and predisposing to graft occlusion.

Prolonged patency in reversed saphenous vein bypass grafts below the popliteal trifurcation has been remarkably good and is equal to or exceeds patency rates for routine femoral popliteal bypass grafts. A consistent increment of increased graft patency and a lower rate of delayed graft thrombosis following femoral tibial bypass with autogenous saphenous vein has been reported by Reichle and Tyson.[21] In their series of 80 patients with femoral popliteal autogenous saphenous vein bypass grafts, 46.3% were alive and had patent veins from 1 to 8 years following femoral popliteal grafting procedure, as compared to 57.1% of 49 femoral tibial bypasses.

Imparato et al.[11] have reported that grafting procedures to the proximal tibial vessel were highly successful if the anterior or posterior tibial artery was patent at least from the level of the midcalf with filling of a portion of the pedal arch. When reconstructions at the level of the malleoli were performed as a result of occlusion of the tibial arteries that extended beyond the midcalf, the graft was successful only if a pedal arch was complete and patent from malleolus to malleolus. These have been the only angiographic criteria so far reported that seemed to have any predictive value in determining patency in attempts at infrapopliteal grafting.

In an interesting study, Nicholas et al.[18] compared two groups of 35 patients each with surgically operable lesions amenable to autogenous vein bypass to arteries distal to the popliteal trifurcation. The groups were treated either with or without the operative procedure. The distal bypass operative procedure increased limb salvage in both the short and long run over the nonoperative group. Mortality for the operative and nonoperative groups was similar at 1 year (16% vs 20%), but within 1 year 65% of the patients not having reconstructive surgery required a major amputation as opposed to only 22% of those having infrapopliteal grafting procedures.

ADEQUACY OF SINGLE-VESSEL REVASCULARIZATION

There is no question that the foot may be adequately revascularized by anastomosis to any one of the infrapopliteal arteries alone. In my experience with the utilization of the anterior tibial, posterior tibial, peroneal, or dorsalis pedis arteries, there has been no instance in which a successful infrapopliteal grafting procedure was attended by unexpected progression of gangrene. Rather the rule has been a rapid demarcation of viable and nonviable tissue after infrapopliteal grafting. Certainly, distal grafting will not revitalize already

dead tissue; thus judgment is required to prevent unnecessary operations on already nonviable limbs. But this is of course no different from the judgment necessary for any other direct arterial surgical procedure.

It is not surprising for a single vessel to be sufficient to maintain circulation in the foot in the light of the proved volume of blood flow that may be obtained through a single-vessel grafting procedure. Bernhard et al.[3] showed that the average baseline blood flow in a femoral-tibial graft was 99 ml/min, compared to an almost identical value of 98 ml/min in a series of femoral-popliteal grafting procedures. In their study, arterially administered papaverine produced an increase in the average flow to as much as 176 ml/min in the femoral-tibial grafts and 162 ml/min in the femoral-popliteal group. These results, showing such high blood flow in the femoral tibial bypass grafts, form at least a partial explanation for the long-term patency and effective relief of ischemia that can be achieved by grafting to any one of the tibial arteries. Interestingly, neither diabetes nor the angiographic or clinical estimations of the severity of arterial occlusive disease correlated with the measured blood flow to the extremity in the series of femoral tibial grafting procedures reported by Bernhard et al.

It is interesting to note that Imparato et al.[11] have reported a lower early patency rate when the peroneal artery is used than when either the posterior or anterior tibial artery is selected for grafting. This difference in patency when the various infrapopliteal vessels are used has not been confirmed by other surgeons and has not been true in my experience. Perhaps the deep, relatively inaccessible position of the peroneal artery that makes it technically the most difficult tibial vessel to use for an anastomosis explains the poor results when this vessel is the site of the distal anastomosis.

DISTAL EXTREMES OF GRAFTING

To date the dorsalis pedis artery is the most distal artery reported to have been successfully used for vascular grafting. To my knowledge, I performed the first anastomosis to the dorsalis pedis artery at The Jewish Hospital of St. Louis in March 1967.[23] I have now used the dorsalis pedis artery as the site for the distal anastomosis of a saphenous vein graft on 13 different occasions. All patients requiring dorsalis pedis grafts have presented with the problem of limb salvage. They have had either rest pain, nonhealing ulcers, or gangrene of a portion of the foot or toe. All patients have been diabetic, and all have had either a myocardial infarction or a cerebral vascular accident previously. Four patients had required amputation of some part of the opposite limb preoperatively, and one required a femoral popliteal bypass graft on the opposite limb postoperatively. Thus significant and widespread vascular disease was present in all these patients.

The results with the use of the dorsalis pedis artery have been very gratifying. Graft patency has been maintained in patients for over 4 years. There have been only two early postoperative graft failures. One occurred in a patient suffering a cerebral vascular accident resulting in spastic crossing of his legs and mechanical occlusion of the graft on his sixth postoperative day. The second failure occurred in a patient in whom the vein selected for bypass graft was found to be recanalized following an unrecognized episide of thrombophlebitis of the saphenous vein. The choice of this vein was obviously an improper one

and such a mistake should not occur again. There has been only one late graft failure; this occurred 3 months postoperatively in a patient who subsequently required a below-the-knee amputation. All the other grafts are either patent at the present time (up to 4½ years postoperatively) or were patent at the time of death of the patients. All deaths in these patients have resulted from progression of vein arteriosclerosis, either myocardial infarction or a cerebral vascular accident.

As a result of the fact that the anterior and posterior tibial and peroneal arteries lie deep in the calf, anastomosis to them can present significant technical difficulties. Since the dorsalis pedis artery has usually been found to be satisfactory in size for anastomosis (usually about 2 mm in diameter), since it is frequently found to be patent, and since it lies superficially in the dorsum of the foot where the technical problems of anastomosis are minimized, I have used this artery preferentially over a patent deep calf vessel on several occasions with good results.

TECHNIQUE

Radiography

Adequate radiographic demonstration of both the distal vessels and of the proximal inflow vessels is an absolute requirement for successful distal arterial grafting. Any compromise of inflow vessels precludes the successful performance of a distal vascular grafting procedure. I have used an automatic cassette changer giving sequential exposures of five 51-inch long cassettes. This technique is usually adequate for the visualization of vessels from the upper abdomen to the dorsum of the foot with a single injection of dye. Repeat injections may be necessary on occasion to correct misjudgments in the timing of the exposures.

A No. 160 Seldinger needle is introduced percutaneously into the common femoral artery on the involved side and approximately 60 ml of 60% iothalamate meglumine (Conray) is injected with a pressure injector at approximately 225 psi or at a rate of about 15 to 20 ml/sec. This allows reflux proximally into the aorta and down both iliac arteries into the thighs, thus giving adequate examination of both legs with a single injection. With the long cassettes exposed at 5 to 10 sec intervals, adequate visualization of the abdomen, thighs, legs, and feet is usually obtained. The first injection is usually performed with the foot in the vertical or slightly externally rotated position. Subsequent injections, usually 30 ml of 60% iothalamate meglumine, are made with hand injections at a slower rate of about 5 to 10 ml/sec, with the foot turned either in full external rotation, giving better visualization of the anterior tibial and dosalis pedis arteries, or in partial internal rotation, opening up the interosseous membrane and giving good visualization of the peroneal vessels.

Operative procedure

Patients have been operated on utilizing either general, spinal, or continuous epidural anesthesia. The entire abdomen and lower extremity are prepared with povidone (Betadine) and draped in the standard sterile fashion. The saphenous vein has been removed through a single continuous long incision, starting in the groin over the saphenofemoral junction and continuing along the course of the saphenous vein down the leg until a segment of vein of a length suitable

to the extent of the required grafting distance has been removed. Other surgeons have elected to use interrupted incision, saving intact bridges of skin in the thigh. As many tributaries as possible are ligated at the time of the removal of the vein. Nonabsorbable sutures, usually Teflon-coated Dacron, are used throughout the procedure. An olive-tip, short metal cannula is inserted and tied into the distal end of the removed vein. Saline solution is injected through the cannula to flush out the blood, to dilate the vein, and to indicate any points of leakage. The leaking tributaries are then ligated with 5-0 ligatures or sutured with 6-0 sutures. Adventitia is then stripped as necessary so that any constricting bands are removed and examination indicates that the vessel is at least 4 to 5 mm in diameter at the narrowest point.

To avoid twisting the graft during the tunneling procedure and thereby occluding the lumen, I have found a longitudinal line drawn with a methylene blue marking pen down the entire length of the graft while it is lying flat on the operating table to be very helpful. This line is invaluable in maintaining orientation of the graft. After marking the graft, it is wrapped in a saline sponge and set aside.

The distal tibial artery to be used for the anastomosis is then exposed. The anterior tibial artery is approached through a longitudinal incision over the anterior muscle compartment. The anterior tibial artery lies just anterior to the interosseous membrane at the lateral edge of the anterior tibial muscle. Multiple small, fragile tributaries are frequently encountered branching from the anterior tibial artery and going to the muscles. These branches must be carefully preserved and not avulsed, or unnecessary and troublesome bleeding will occur after the anastomosis has been completed.

The posterior tibial and peroneal arteries are exposed in the midcalf through a medial incision just posterior to the tibia. The tibial attachments to the soleus muscle are cut, and the fascial plane is entered deep to the soleus muscle. The posterior tibial and peroneal arteries both lie in this plane and are easily exposed. The peroneal artery lies further lateral and deeper in the incision, making anastomosis to it somewhat more difficult than to the somewhat more superficial posterior tibial artery. Occasionally the site selected for the posterior tibial anastomosis is just superior and/or posterior to the medial malleolus. The posterior tibial artery in this area lies quite superficially and is easily utilized for anastomosis. This area is a preferential site for anastomosis to the posterior tibial artery whenever possible.

The distal anastomosis is always performed first, since it is usually the more difficult anastomosis. The extra freedom given by being able to freely manipulate the saphenous vein aids in the performance of the anastomosis. Just prior to the occlusion of the tibial vessel selected for grafting, systemic heparinization with 6000 to 7000 units of intravenous heparin is instituted. The vessel is clamped using two small, smooth Schwartz neurosurgical clips. A 2- to 3-power loupe having a convenient focal length and sufficient depth of field is used in all anastomoses. A longitudinal incision approximately twice the diameter of the vein is made in the distal artery and a standard "fish-mouth" anastomosis as originally described by Kunlin et al.[14] is performed using 6-0 Teflon-coated Dacron sutures. I have found the use of ophthalmologic needle holders and tissue forceps to be a great aid in the performance of the

small anastomoses. I have used an operating microscope on occasion, but find that it does not aid in the technical performance of the anastomosis and frequently detracts from the operative procedure because it is cumbersome and immobile. The final sutures are not tied but allowed to lie loosely in place, maintaining an open site in the anastomosis for later flushing of the graft. The graft is then tunneled up to the proximal site of anastomosis at the common femoral artery, following the normal course of the femoral and popliteal arteries. Thus the tunnel runs from the common peroneal artery, deep to the sartorius muscle, into the popliteal space, between the heads of the gastrocnemius muscle, and behind the fibers of origin of the soleus muscle. Grafts ending at the posterior tibial artery just posterior to the medial malleolus are passed in the subcutaneous plane to approximately the middle of the calf; they are then passed through the fascia of the calf behind the medial head of the gastrocnemius muscle and into the popliteal space and then up to the common femoral artery.

The proximal anastomosis is performed in the standard "fish-mouth" fashion. Usually the common femoral artery just at or above the profundus femoris branch is the site of election for the proximal anastomosis. Infrequently the superficial femoral artery itself is used or an endarterectomized segment of the superficial femoral artery is used. On occasion, when there is minimal evidence of arteriosclerosis in the superficial femoral artery (as has been encountered in many of the diabetic patients) and when the distal anastomosis is to the dorsalis pedis artery, the proximal popliteal artery has been used as the proximal site of anastomosis.

After both anastomoses have been constructed, the graft is flushed through the partially opened distal anastomosis. When assured that a satisfactory pulse is present throughout the graft, the distal anastomosis is completed by tightening the previously placed but untied sutures. The wounds are then closed in layers with interrupted sutures, closing the superficial fascia of the thigh and subcutaneous tissues of the leg. The skin is closed with fine, interrupted, nonabsorbable sutures.

When the dorsalis pedis artery is utilized, the exposure is somewhat different. A curvilinear incision is started on the dorsum of the foot beginning in the interosseous space between the first and second metatarsal bones. This incision is curved anteriorly to the medial malleolus over the saphenous vein and then up the course of the saphenous vein. Not only is the saphenous vein removed through this incision, but the dorsalis pedis artery is also exposed through the distal portion of the same incision. The distal anastomosis is made as previously described. The graft is then brought medially, anterior to the medial malleolus in the subcutaneous tissue, in the plane from which the saphenous vein has just been removed. At the midcalf the vein is then brought through the crural fascia, passing deep to the medial head of the gastrocnemius muscle and into the popliteal space. It is then tunneled superiorly as described previously. The skin over the graft is closed, carefully avoiding the possibility of mechanically occluding the graft between the skin and the bony malleolus by using multiple, carefully placed sutures in the subcutaneous tissue and in the skin.

Sympathectomy has not been performed in any of the patients, and I have not found it to be an aid in maintaining the patency of any femoral popliteal grafting procedure. No postoperative anticoagulation or dextran has been used.

Ambulation has been allowed on the first postoperative day. Postoperative edema has been controlled with elevation of the leg, diuretics, sodium limitation, and occasionally, if persistent, with elastic stocking support. I have not used routine postoperative prophylactic antibiotics. However, appropriate antibiotics have been used when open ulcers or infections in the feet were present. The choice of antibiotics is dictated by the sensitivity results of the culture of the infected material.

Fig. 13-1. A, Preoperative view of foot showing gangrene of third toe. B, Six weeks postoperatively showing autoamputation of third toe and complete healing of stump.

ILLUSTRATIVE CASES

Case I: Use of dorsalis pedis artery. Q. E., a 75-year-old, alert, and cooperative woman, was referred to The Jewish Hospital of St. Louis because of gangrene of the right third toe and rest pain involving the entire right forefoot (Fig. 13-1, *A*) with the suggestion from her physician that the right foot be amputated. She was a known diabetic on oral antidiabetic medication and had had a myocardial infarction about 2 years prior to her admission. A femoral arteriogram showed marked sclerotic changes in the right superficial femoral artery with multiple areas of marked stenoses and occlusion of the distal popliteal artery. The dorsalis pedis artery was patent and appeared smooth and free of arteriosclerotic plaques. A reversed saphenous vein graft taken from the same leg was inserted from the right common femoral artery to the dorsalis pedis artery (Fig. 13-2). Immediately postoperatively the right

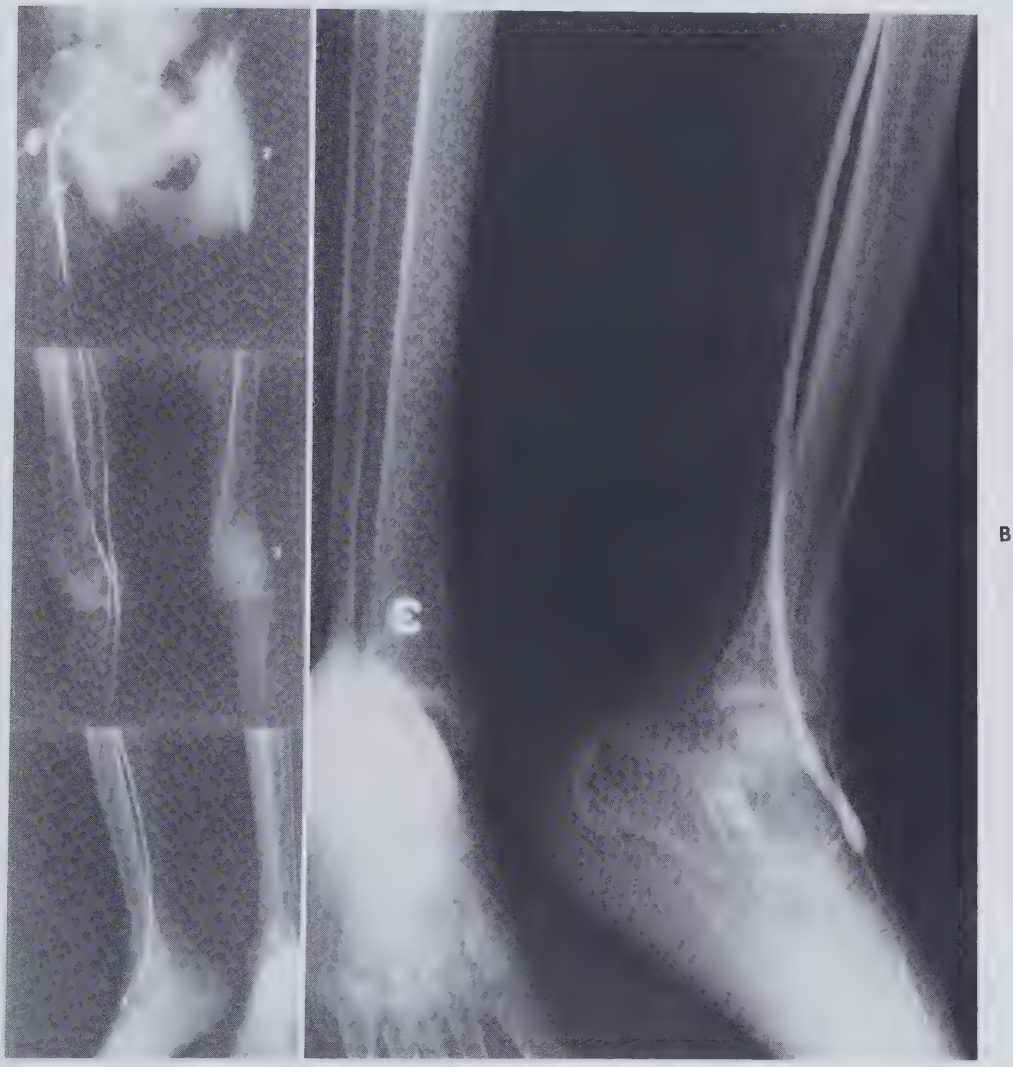

Fig. 13-2. A, Postoperative arteriograms showing femoral-dorsalis pedis graft. **B,** Close-up of dorsalis pedis graft. Note valve in vein above malleolus.

Fig. 13-3. Postoperative arteriogram with foot in moderate inversion showing peroneal artery lying between tibia and fibula.

foot appeared revascularized; it was warm and the rest pain disappeared. Within 6 weeks the gangrenous toe autoamputated itself and the stump healed (Fig. 13-1, *B*). The patient did well for about 1 year, at which time she suffered a cerebral vascular accident, leaving her left (unoperated) lower extremity markedly paralytic. Because her right foot was strong and useful, she was able to ambulate with the aid of a cane. About 2½ years postoperatively she suffered a massive myocardial infarction and died.

Case II: Use of peroneal artery. T. M., a 76-year-old man, was admitted to The Jewish Hospital of St. Louis because of an enlarging ulcer over the head of the left fifth metatarsal. He was a known diabetic on diet and oral antidiabetic medication for over 9 years. Eight years prior to admission he had had a myocardial infarction and had been taking digitalis since then. During the 6 weeks prior to his admission to the hospital an ulcer over the left fifth metatarsal head appeared and steadily enlarged. It extended onto the lateral aspect of the left toe and was associated with increasing pain. On examination he demonstrated

Fig. 13-4. Postoperative arteriogram showing graft to large posterior tibial artery.

strong femoral and popliteal pulses but no dorsalis pedis or posterior tibial pulses in either leg. The examination was corroborated by the arteriogram that showed patent superficial femoral and popliteal vessels bilaterally with infrapopliteal occlusion. The peroneal artery was opened in the distal calf of the left foot. A reversed saphenous vein bypass graft was inserted from the proximal popliteal artery to the peroneal artery in the midcalf (Fig. 13-3). Immediately postoperatively the ulcer showed signs of healing. He was discharged on his ninth postoperative day to return 1 month later. At that time the left fifth toe was amputated and there was immediate healing of the amputation site. The graft remained patent for the remaining 3 years of the patient's life. He finally died of a cerebral vascular accident.

Case III: Use of posterior tibial artery. B. D., a 77-year-old man, has been a known diabetic for many years. He is markedly hypertensive, and an old myocardial infarct is evident on his electrocardiogram. About 6 weeks prior to admission he developed cellulitis of his left foot, requiring treatment with antibiotics. One month before he was admitted to

The Jewish Hospital of St. Louis, he developed an ulcer over the dorsum of the left middle toe. The ulcer enlarged and became quite painful, and the patient was referred to The Jewish Hospital of St. Louis for therapy. Arteriograms showed the superficial femoral and popliteal artery on the left to be occluded. The posterior tibial artery was patent and quite large. A reversed saphenous vein bypass graft starting at the left common femoral artery was inserted down to the posterior tibial artery just above the medial malleolus (Fig. 13-4). He was discharged from the hospital 13 days postoperatively. The ulcers healed within 6 weeks and his progress has been followed, reports indicating no pain and a patent graft for the 8 months since opration.

SUMMARY

Bypass grafting to arteries below the popliteal trifurcation is an effective means of limb salvage in the selected cases. The procedure requires extensive, careful preoperative arteriographic study to delineate patent vessels and careful, meticulous surgical technique for success. When these criteria are met, both short- and long-term patency rates are high, and revascularization of the limb is readily accomplished. Thus it would seem that infrapopliteal bypass grafting is a reasonable alternative to amputation, even though modern rehabilitative techniques for amputees have been greatly improved.

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14

Surgical treatment in extracranial cerebral arterial insufficiency

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Extracranial cerebral arterial insufficiency most commonly results from arteriosclerotic occlusive disease. Less frequent causes include cerebral arterial embolization associated with cardiac disease, occlusion resulting from dissecting aneurysm, trauma, fibromuscular hyperplasia, and occlusive arteritis. All of these processes may be associated with varying degrees of brachiocephalic ischemia.[19] This chapter will confine itself to surgical treatment for extracranial arterial insufficiency resulting from arteriosclerotic occlusive disease.

RATIONALE FOR SURGICAL TREATMENT

Cerebral arterial insufficiency often results from extracranial disease and is frequently correctable by surgery. The true incidence of extracranial disease among unselected patients with arteriosclerotic cerebrovascular disease is unknown. The majority of patients are less than 65 years of age, and men are affected at least twice as frequently as women.[8] Patients with hypertension, diabetes, and generalized arteriosclerosis have an increased incidence of cerebral arterial insufficiency, often resulting from extracranial disease. Results of the *Joint Study of Extracranial Arterial Occlusion* indicated that 75% of 3788 patients in whom four vessel studies were performed had extracranial cerebral arterial lesions that were surgically accessible.[11] The most common sites for extracranial cerebral arterial disease are demonstrated in Fig. 14-1.

Established principles regarding arterial insufficiency in other parts of the body support the concept that partial obstruction of extracranial arteries to the brain represents a cause of ischemia, which may be intermittent or permanent depending on the hemodynamic conditions and the status of the collateral circulation. The relative importance of the carotid and vertebral systems is placed in

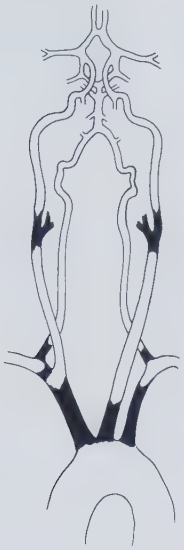

Fig. 14-1. Frequent sites for extracranial arterial obstruction resulting from arteriosclerotic occlusive disease.

perspective by recognition of the normal blood flow and the capacity for blood flow in each of those systems. As much as 90% of total cerebral blood flow may be through the two internal carotid arteries as measured by an electromagnetic flowmeter in anesthetized patients.[23] With occlusion of the carotid system, the vertebral system assumes more importance and may, in complete carotid occlusion, be the only effective supply to the brain. Vertebral flow in such instances has been found to be as much as 80% of total normal flow as measured by the nitrous oxide technique.[23]

Since many patients with extracranial arterial disease have normal cerebral hemodynamics under basal conditions as measured by the Kety-Schmidt technique, the suggestion has been made that carotid or vertebral insufficiency represents a potential problem. Reduction of blood flow from a slowly developing stenosis prior to actual occlusion is rarely a cause in production of a frank stroke except in the instance of acute hypotension, although transient symptoms related to reduced flow may occur.[26] Total cerebral blood flow may remain unchanged after surgical relief of obstructing lesions in many such patients.[7] The significant fact is that even though total cerebral flow may remain unchanged, most patients will have an increase in flow in the artery relieved of obstruction and therefore an increase in reserve flow capacity. Engell[7] found that following carotid endarterectomy 82% of patients had increased flow in the artery operated on, as evidenced by the artery supplying about 50% more brain tissue than before operation.

A high incidence of ulceration in atheromatous plaques of the carotid bifurcation has been recognized as a potential source of thrombosis and embolization.[17] Intermittent embolization may represent the major cause of transient ischemic attacks. Certainly emboli in the retinal vessels have been documented

in patients with carotid bifurcation atheroma.[15] Rough carotid plaques have been observed more frequently in patients with greater than 50% stenosis of the internal carotid artery than in patients with lesser degrees of stenosis.[10] Intimal ulceration may, however, be found in the absence of an arteriographic defect, and it is relatively unusual to be able to establish the fact of ulceration radiographically.[16]

The rationale for surgical treatment of patients with extracranial arterial lesions is the prevention of ischemic attacks related to embolization from ulcerated plaques or to obstruction of flow by the lesions. Furthermore, stenotic carotid lesions may lead to complete occlusion and stroke. Wylie and Ehrenfeld[26] found that over 50% of patients studied after completed stroke were found to have occlusion of the appropriate internal carotid artery. That stroke may occur in the absence of progression of the lesions if the patient experiences profound hypotension is well recognized.

A strong indication for surgical treatment can be based on the prevention of transient symptoms of cerebral arterial insufficiency. Patients with correction of carotid stenosis in the presence of bilateral carotid disease have been observed to have a significantly decreased incidence of transient ischemic attacks when compared with nonsurgical patients ($p = 0.025$).[9] This difference is more striking when carotid endarterectomy is evaluated in patients with complete occlusion of one carotid artery ($p < 0.001$).

CLINICAL PATTERNS

Patients with cerebral arterial insufficiency may be classified according to the presence or absence of symptoms. Transient cerebral ischemia (transient ischemic attacks or transient neurologic disturbance) is characterized by one or more brief temporary episodes of neurologic dysfunction that are usually focal. It has been estimated that nearly half of untreated patients with transient ischemic attacks will eventually have a completed stroke.[26] Completed stroke (frank stroke) implies cerebral infarction and permanent neurologic dysfunction, which may remain fixed, improve, or worsen. Such patients may subsequently develop additional symptoms that are transient. The term "reversible ischemic neurologic deficit" has been used to describe an intermediate state between transient ischemic attacks and completed strokes.[26] Finally, a smaller group of patients with extracranial cerebral arterial disease are asymptomatic and are usually suspected of having extracranial disease by the presence of a murmur over the stenotic artery. When a careful history is taken, some "asymptomatic" patients are actually found to have decreased memory or impaired mentation. The term "chronic cerebral ischemia" has been used to identify patients with memory loss, impaired mentation, or mental deterioration without focal disorders.[25]

Lesions involving the carotid bifurcation represent the most common extracranial site and are classically associated with unilateral motor and sensory symptoms, aphasia, and monocular blindness. Lesions involving the subclavian-vertebral-basilar system are often associated with dizziness, syncope, vertigo, diplopia, bilateral visual disturbance, tinnitus, and ataxia. Carotid artery stenosis may be associated with any of the aforementioned symptoms, since the carotid system is the more important one in the maintenance of adequate cerebral flow. Many patients with both carotid and vertebral artery disease and classic symp-

toms of vertebral-basilar insufficiency may be relieved by correction of the carotid stenosis alone. The pattern of extracranial arterial insufficiency resulting from internal carotid artery stenosis has been explained on a basis of reduced carotid flow or of embolization from ulcerating plaques. Complete occlusion or stenosis of the common carotid arteries or innominate artery are more unusual patterns.

Although symptoms of cerebral insufficiency may occur with bilateral vertebral artery stenosis or occlusion, stenosis of one vertebral artery only is rarely responsible for symptoms when carotid stenosis is not present. An important cause of vertebral-basilar insufficiency is obstruction of the subclavian or innominate

A

Continued.

Fig. 14-2. A, Arteriogram demonstrating retrograde flow in left vertebral artery and proximal occlusion of left subclavian artery following injection into right subclavian artery. **B,** Flow measurements taken during operation in same patient confirming retrograde flow in left vertebral artery under basal conditions.

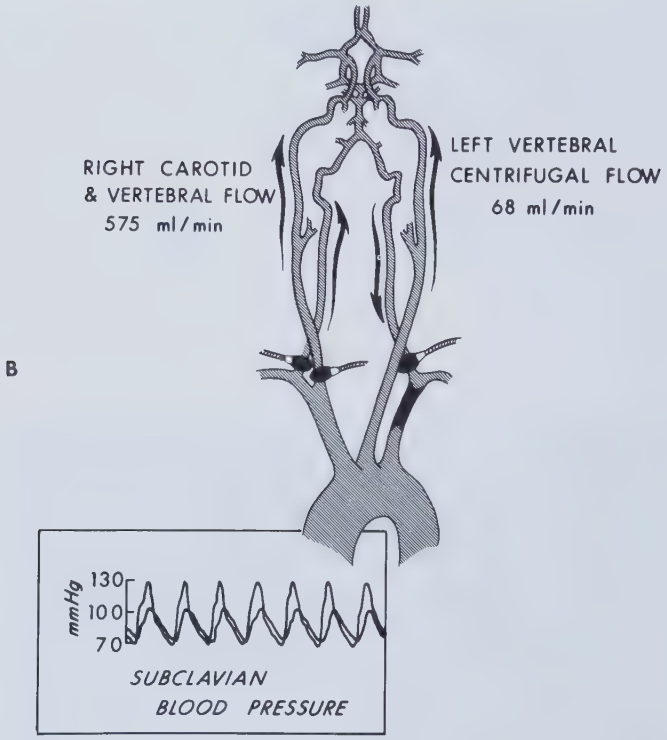

Fig. 14-2, cont'd. For legend see p. 361.

arteries. The importance of retrograde vertebral flow was recognized by Smyth,[24] who ligated the right vertebral artery in a patient with multiple attacks of syncope in association with hemorrhage from a recurrent subclavian aneurysm following previous successful ligation of the innominate and carotid arteries. Nearly a century later, Contorni[3] observed retrograde vertebral flow in a patient with arteriosclerotic obstruction of the subclavian artery. Rob[21] later reported relieving symptoms of cerebral arterial insufficiency in a patient with retrograde vertebral flow by ligating the vertebral artery. Reivich et al.[20] firmly established the association of retrograde blood flow in the vertebral artery with symptoms of cerebral insufficiency. This hemodynamic phenomenon has been referred to as the "subclavian steal syndrome."

Most patients with "subclavian steal" experience transient ischemic attacks consisting of dizziness, vertigo, weakness, visual disturbances, syncope, tinnitus, or other generalized cerebral symptoms.[12] Approximately half of the patients will have some symptoms of ischemia related to the arm. Arm claudication is more commonly seen in the younger and more active patients with this syndrome. The subclavian stenosis or occlusion is usually on the left and characteristically results in a systolic blood pressure differential of 20 mm Hg or more in the arms. Most patients have a murmur in the upper chest or lower neck. Fig. 14-2 demonstrates flow measurements taken during operation in such a patient. Although this syndrome may occur with a single subclavian obstruction

Continued.

Fig. 14-3. Aortogram demonstrating, **A**, antegrade flow in left common carotid artery and in left subclavian and vertebral arteries and, **B**, retrograde flow in right common carotid artery and right vertebral artery as a result of occlusion of the innominate artery. **C**, Hemodynamic pattern in same patient.

in the absence of other extracranial arterial lesions, my experience suggests that most patients also have associated carotid artery stenosis, which may be the more significant cause of cerebral arterial insufficiency.[12]

A more severe pattern of extracranial cerebral arterial obstruction occurs with occlusion of the innominate artery. Obstruction to forward flow through the right common carotid and subclavian arteries is compounded by retrograde flow in these arteries.[2] This phenomenon has been termed the "innominate steal." Fig. 14-3 illustrates this pattern.

An even more severe "steal" phenomenon is illustrated in Fig. 14-4 and

B

Fig. 14-3, cont'd. For legend see p. 363.

A

Continued.

Fig. 14-4. Aortogram demonstrating, **A**, complete occlusion of right common carotid, left common carotid, and left subclavian arteries. The right vertebral artery is enlarged. **B**, Retrograde flow is observed in left vertebral and left internal carotid arteries with flow into external carotid artery. **C**, Hemodynamic pattern in same patient. **D**, Operation consisted of Dacron bypass from ascending aorta to carotid bifurcation on left and bypass to left subclavian artery. Right internal carotid artery was occluded. **E**, Aortogram 6 weeks following operation demonstrating patent bypass grafts.

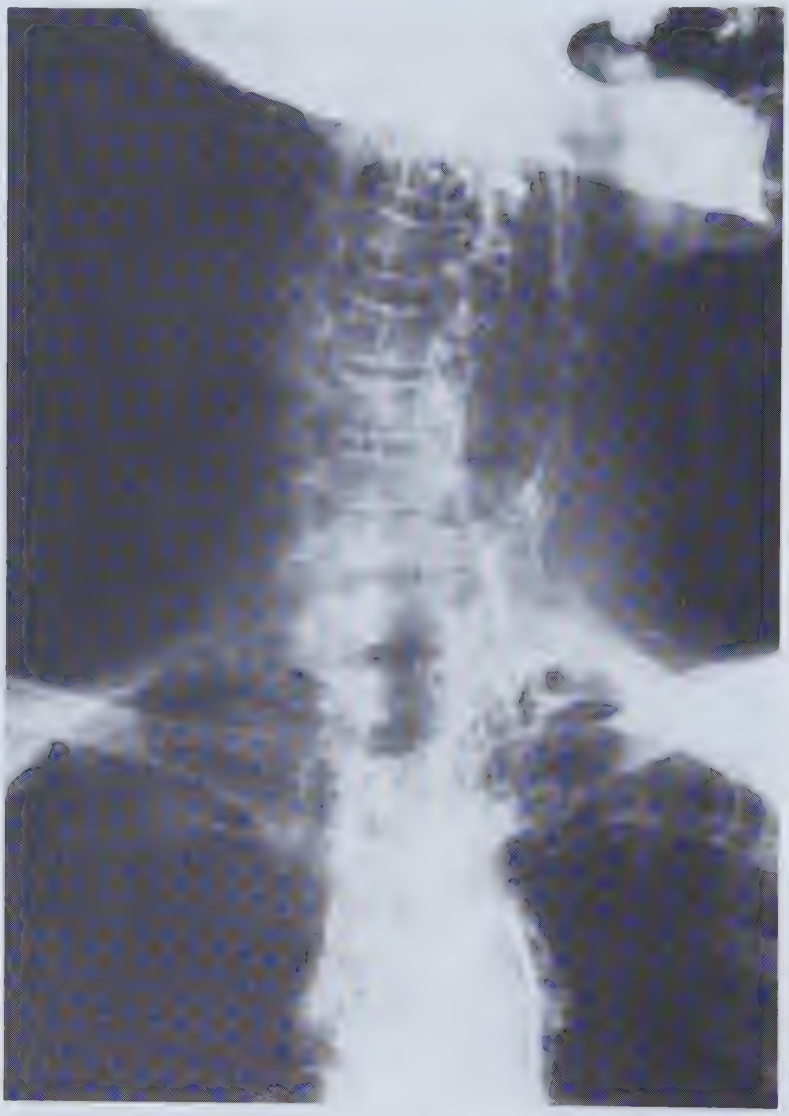

Fig. 14-4, cont'd. For legend see p. 365.

emphasizes the capacity for flow of a single vertebral artery. Obstruction of the right common carotid artery, left common carotid artery, and left subclavian artery resulted in all the cerebral flow being afforded through the right vertebral artery. Retrograde flow occurred in the left vertebral artery and in the left internal carotid artery into the external carotid artery.

Another "steal" phenomenon may occur with occlusion of the common carotid artery. With this occlusion about half of the patients will have retrograde flow from the internal carotid artery into the external carotid artery, depending on the peripheral resistance and flow into each artery.[7] This pattern is also demonstrated in the arteriogram in Fig. 14-4.

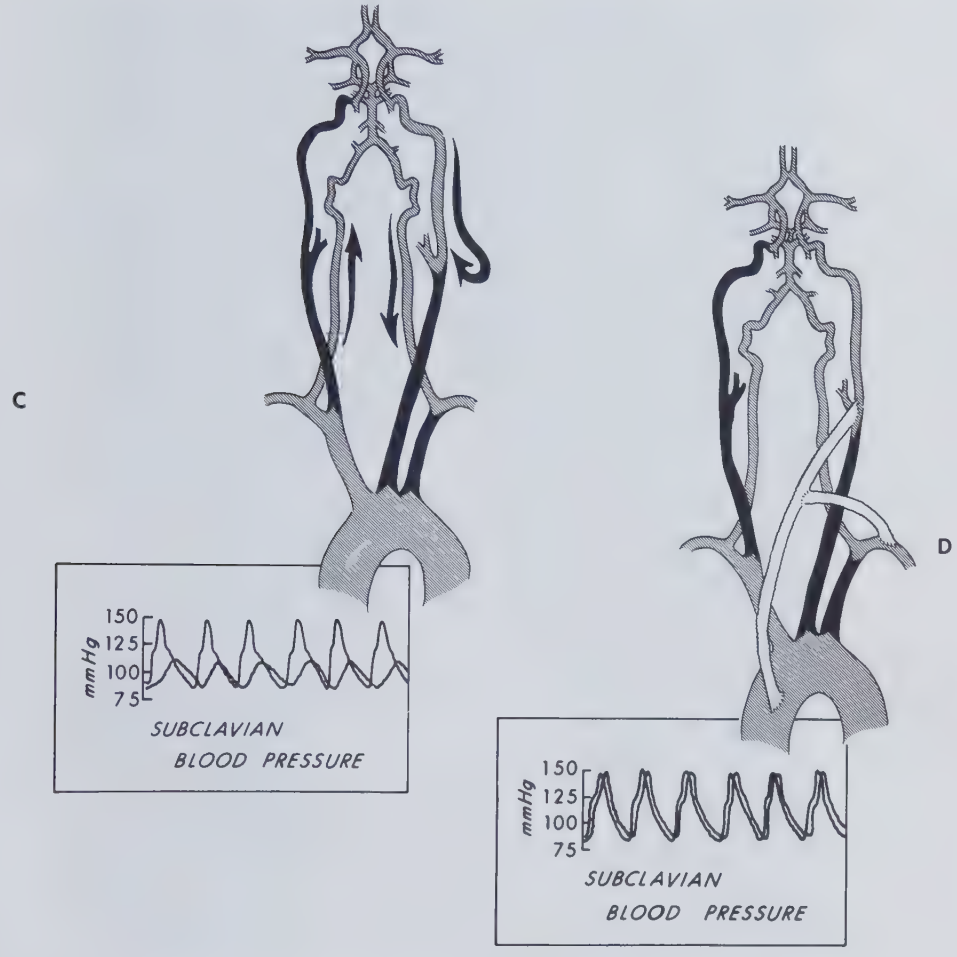

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Fig. 14-4, cont'd. For legend see p. 365.

ARTERIOGRAPHY

Indications

The presence of extracranial arterial disease may be strongly suspected by the patient's symptoms and by physical examination. The presence of a murmur over the carotid bifurcation nearly always indicates disease of the carotid bifurcation and usually indicates stenosis of the internal carotid artery. Murmurs are frequently present with stenosis of the common carotid, innominate, and subclavian arteries. A blood pressure differential in the arms is usual with significant subclavian or innominate stenosis. Suspicion of significant extracranial arterial stenosis or occlusion should prompt arteriography. Arteriography is generally deferred in most patients with acute stroke for a period of 3 to 6 weeks except in the unusual instance where emergency carotid endarterectomy is indicated, as will be discussed in a subsequent section.

Fig. 14-4, cont'd. For legend see p. 365.

Technique

Arteriography is generally performed through a transfemoral route. This technique permits selective injection of the carotid and subclavian arteries and visualization of the aortic arch. The importance of adequate visualization of the origins of the innominate, carotid, and subclavian arteries and visualization of the intracranial circulation cannot be overemphasized. Serial exposures will permit visualization of the extracranial and intracranial arteries and demonstrate the status of collateral circulation. Views of the neck and cranial arteries should be taken in both anteroposterior and lateral planes, and views of the aortic arch and great arteries should be taken in both oblique projections.

When the transfemoral technique is impossible as a result of occlusion of the aorto-iliac system, retrograde axillary catheterization may be done. This approach often also requires direct injection of the left common carotid artery. Direct

carotid injections and direct subclavian or retrograde brachial injections are seldom performed because of the advantages of retrograde catheter technique.

THE OPERATION

Indications

The presence of disease at the carotid bifurcation is the most common indication for operation, and carotid endarterectomy is the most common operation. Lesions determined by arteriography to obstruct half of the lumen of the internal carotid artery are considered hemodynamically significant for the reasons discussed. Fig. 14-5 illustrates such a lesion. Lesions of lesser hemodynamic significance may be the cause of emboli, accounting for transient ischemic attacks. Fig. 14-6 illustrates an ulcerated plaque in such a patient. The presence of transient cerebral ischemia and a demonstrable plaque of any size may be indication for carotid endarterectomy in certain patients. When bilateral internal carotid artery stenosis is present and of comparable significance in a patient with symptoms that are not localized, the artery supplying the nondominant hemisphere is operated on first.[1] If one carotid artery is markedly more stenotic than the other, the most severe stenosis is corrected initially. If symptoms have been localized, the artery to the symptomatic hemisphere is usually operated on first.

Lesions that completely occlude the innominate, common carotid, and subclavian arteries are usually indications for reconstruction. Stenotic lesions of these arteries may also be indications for correction if the stenosis is significant as indicated by symptoms, arteriography, murmur, or blood pressure differential. Since proximal obstructing lesions should be repaired before distal obstructing lesions in the same system, significant lesions of the innominate or either common carotid artery should be relieved prior to relief of stenosis of the carotid bifurcation. Generally a stenosis or occlusion proximal to a distal total occlusion is corrected if there is expectation that collateral circulation may be significantly improved. The absence of potential intervening collateral circulation would not be an indication for operation such as relief of an internal carotid stenosis at the bifurcation when the internal carotid was occluded or nearly occluded more distally.

Patients with combined carotid stenosis and obstructions of the ipsilateral subclavian artery may have correction of both during the same operation with the use of an extrathoracic approach for the subclavian artery. Although carotid-subclavian bypass is usually combined with carotid endarterectomy when indicated, carotid endarterectomy alone results in complete relief of transient ischemic attacks in selected patients. This approach has been used in some elderly patients who had no symptoms of arm ischemia related to the subclavian obstruction.

Unilateral stenosis of one vertebral artery is seldom if ever an indication for operation if both internal carotid arteries appear normal and the opposite vertebral artery appears adequate. The flow capacity of an open carotid system in combination with one vertebral artery does not appear to support hemodynamic significance to an isolated vertebral stenosis. Before attributing a patient's symptoms to an isolated vertebral stenosis, care must be taken to exclude an intracranial arterial obstruction or other possible cause. Bilateral vertebral stenosis associated with symptoms is sometimes an indication for the repair of one vertebral artery. Many patients with internal carotid artery stenosis, unilateral

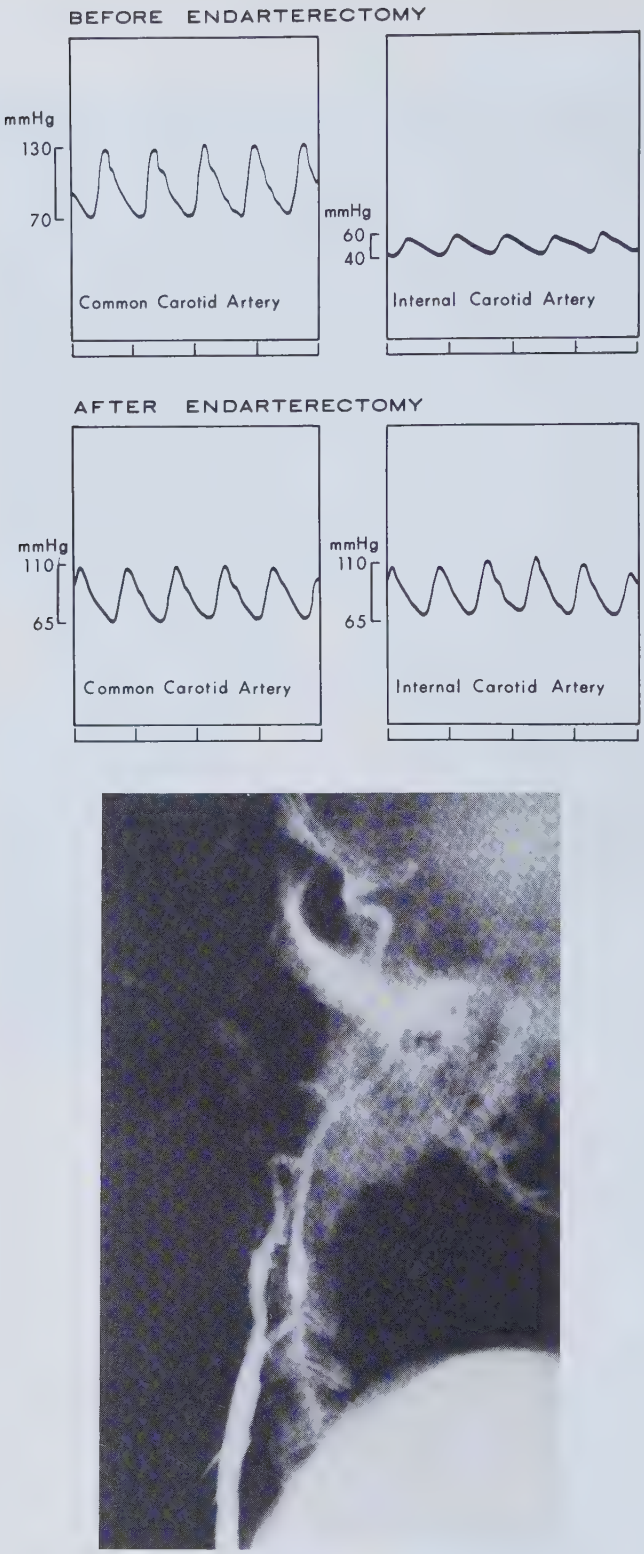

Fig. 14-5. Carotid arteriogram and pressure tracings taken proximal and distal to severe internal carotid stenosis during operation.

A

Continued.

Fig. 14-6. A and **B,** Arteriogram demonstrating ulcerated plaque at carotid bifurcation. Internal and external carotid arteries are well visualized. Ulcer is best visualized in anteroposterior projection. It is extremely unusual to demonstrate ulceration in a plaque this clearly on an arteriogram. **C,** Photograph of ulcer and plaque.

or bilateral, combined with bilateral vertebral artery stenosis are relieved completely by appropriate carotid endarterectomy.

The argument for operation in patients with asymptomatic carotid stenosis is based on the propensity for such lesions to increase in degree and the possibilities of sudden occlusion of an internal carotid artery and stroke. The argument is strongest in patients with bilateral carotid disease, in patients with total occlusion of one carotid artery, and in patients with a severe carotid stenosis who are to undergo a surgical procedure that might be attended by hypotension.[22, 25, 26] Thompson et al.[25] noted that in following 37 patients with asymptomatic carotid stenosis for an average of about 24 months, 14 developed transient ischemic attacks and 10 developed frank strokes, 9 of which were believed to result from total occlusion of the internal carotid artery.

Acute stroke. Carotid endarterectomy is *infrequently* indicated in patients with an acute stroke.[16, 22, 25, 26] The risks of emergency carotid endarterectomy for acute stroke do not justify the possible benefits in most instances. The possibility of intracerebral bleeding as a result of restoring flow to an infarcted area is a major consideration. Experience suggests that operation should be deferred

B

Fig. 14-6, cont'd. For legend see p. 371.

for a period of 3 weeks or more following acute stroke. Generally arteriography is also deferred for at least 3 weeks. The indications for deferred operation in such patients include transient ischemic attacks in addition to existing neurologic deficit, carotid stenosis contralateral to an occluded internal carotid artery, or the existence of an extracranial stenosis or occlusion, relief of which might be expected to result in significant improvement in cerebral blood flow or cerebral blood flow capacity.

Rob[22] has suggested that the results of emergency carotid endarterectomy for acute stroke might be improved if patients are operated on early. Operation is sometimes justified if the patient has been symptomatic for less than 6 to 8 hr.[26] Patients with symptoms for more than 12 hr probably should not be operated

C

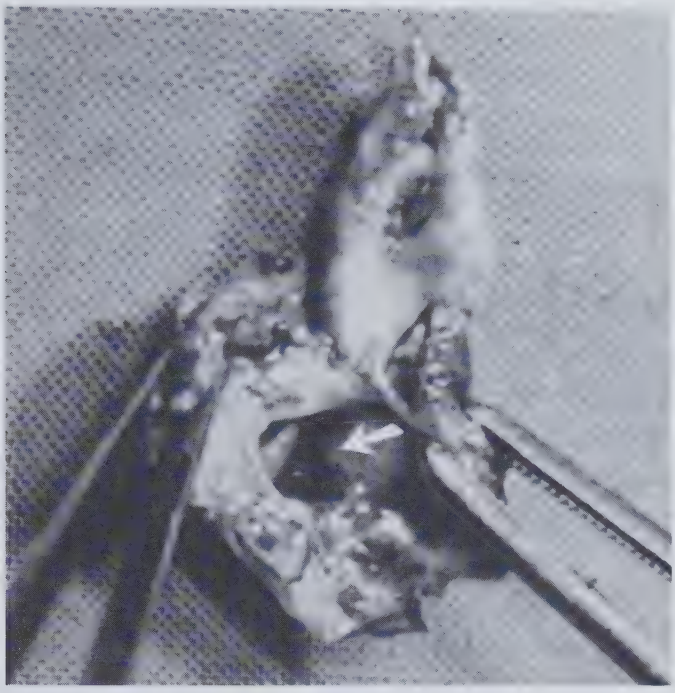

Fig. 14-6, cont'd. For legend see p. 371.

on.[23] The clearest indications for emergency endarterectomy are in patients who develop internal carotid occlusion and stroke while in the hospital or following carotid arteriography in instances where the diagnosis is established promptly.

Complete occlusion of an internal carotid artery. Operation is sometimes indicated for an acutely occluded internal carotid artery under the circumstances previously outlined. Operation is not indicated for long-standing occlusion of the internal carotid artery.[25, 26] Restoration of flow is not usually practicable, and the possible risks of embolization or injury to the internal carotid artery do not justify the remote possibility of improvement related to the restoration of flow.

Anesthesia

General anesthesia is preferred to local anesthesia. The major advantages of general anesthesia are controlled ventilation and assurance of adequate respiration, decrease in cerebral oxygen consumption, and patient comfort. Adequate arterial oxygen tension must be maintained throughout operation and especially when a major artery is temporarily occluded, as during carotid endarterectomy. Control of arterial CO_2 tension is also important. Although hypercapnia increases total cerebral blood flow by increasing systemic pressure and decreasing total cerebrovascular resistance, regional cerebral blood flow may be decreased.[7] The arteries of an ischemic region are already dilated, and a decrease in total cerebrovascular resistance may result in decreased perfusion pressure in the collaterals supplying the ischemic zone so that an "intracerebral steal" occurs. Furthermore, hypercapnia may produce an increase in cerebral venous pressure, resulting in a

decrease in cerebral arterial-to-venous pressure gradient and therefore a decrease in perfusion pressure. Although hypercapnia in practical application may have no significant influence on the result of operation, there appears to be no advantage to its use. At constant systemic pressure, hypocapnia provides the highest perfusion pressure and flow to the brain.[6] Larsen[18] has recommended the maintenance of P_{aCO_2} between 20 and 25 mm Hg during carotid endarterectomy.

Hypotension should be avoided during operative occlusion of the carotid artery. Rarely small doses of an alpha-adrenergic agent administered as an intravenous infusion may be required to maintain systemic arterial pressure at normal levels. No effort is made to increase blood pressure above normal levels.

Surgical technique

Carotid endarterectomy. With the patient in a supine position and the neck extended and rotated to the opposite side, a longitudinal incision is made along the anterior border of the sternocleidomastoid muscle (Fig. 14-7). The sternocleidomastoid muscle is reflected laterally, and the common facial vein is ligated and divided, allowing the jugular vein to be retracted posteriorly. The common facial vein is usually at the approximate level of the carotid bifurcation. The common carotid artery is dissected and encircled with a tape. The descending branch of the hypoglossal nerve may be sacrificed without concern. The hypoglossal nerve is identified and retracted gently cephalad as the internal carotid and external carotid arteries are encircled. The superior thyroid artery, the first branch of the external carotid, or commonly a branch at the junction of the common and external carotid arteries is also encircled; on occasion the ascending pharyngeal or other external carotid branches are also isolated. The internal carotid artery is dissected to the base of the skull and mobilized completely. The origin of the external carotid is mobilized, but it is unnecessary to mobilize the medial wall of the carotid bifurcation.

Particular care should be taken in retracting the hypoglossal nerve to prevent undue traction and temporary nerve injury. Similarly, care should be taken in the retraction of the superior part of the wound to avoid excessive pressure on the marginal mandibular branch of the facial nerve. The vagus nerve should be identified and protected along its close relationship to the common carotid artery and to the internal carotid artery.

Heparin is injected systemically or into the internal jugular vein (5000 to 7500 units) and, after a 3 to 5 min period, the common carotid artery is occluded with a vascular clamp. The internal and external carotid arteries are also occluded with vascular clamps, and the internal carotid is occluded as far distally as possible, well beyond the plaque. An incision is made in the common carotid artery and extended for about 1 mm into the internal carotid artery. The occluding plaque and thickened intima are then dissected from the wall of the common carotid artery and transected proximally. The endarterectomy is then continued distally into the external carotid artery, and the plaque is removed from the lumen of the external carotid by gentle traction. Finally, the endarterectomy is completed in the internal carotid artery. Gentle traction on the plaque will intussuscept the internal carotid artery so that a double thickness of smooth intima is visualized about the distal plaque. The plaque removed from the internal carotid artery characteristically has an iceberg configuration. The endarterectomy site

Fig. 14-7. Operative approach for carotid endarterectomy.

is cleaned of any debris and irrigated with saline solution. The arteries are flushed by momentarily removing each vascular clamp. The arteriotomy is closed with a continuous running suture of 00000 vascular suture; the vessels are allowed to fill with blood, expelling all air before the final sutures. The clamp is generally removed from the external carotid artery first and then the common carotid artery before removing the internal carotid artery clamp. The heparin is neutralized with protamine. Neutralization with protamine is not always necessary but should be routinely done in hypertensive patients.

A patch is not required in repair of the arteriotomy except in unusual instances where the plaque has eroded the wall of the bifurcation, causing an aneurysm (Fig. 14-8), or where the arteriotomy must be extended for some distance into the internal carotid artery. Patching is only rarely necessary. An internal shunt is not used even when the opposite carotid artery is totally occluded if the verte-

Fig. 14-8. A, Arteriogram demonstrating internal carotid stenosis. B, Photograph at operation in same patient demonstrating erosion of plaque and early aneurysm formation at bifurcation.

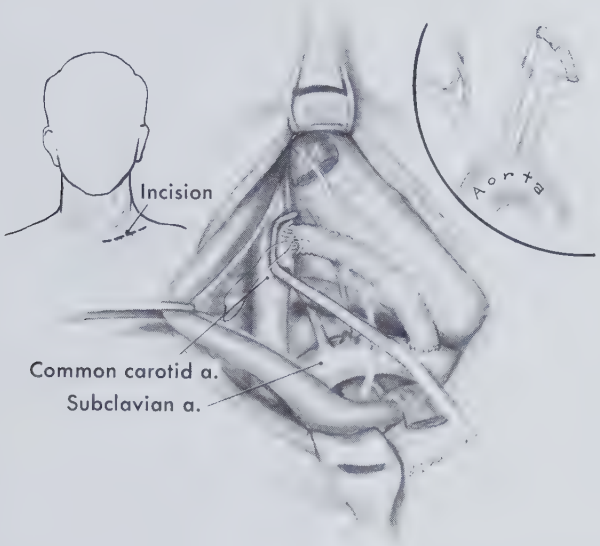

Fig. 14-9. Approach for common carotid-subclavian bypass.

bral-basilar system appears adequate on arteriography and the major intracranial arterial circulation appears intact.

As previously mentioned, the medial wall of the carotid bifurcation is not mobilized, since complete mobilization of the bifurcation is not necessary and may result in bradycardia and hypotension as a result of carotid sinus stimulation. The carotid sinus reflex can generally be prevented by adequate premedication with atropine or scopolamine and careful dissection. The reflex may be abolished by local infiltration of lidocaine (Xylocaine) beneath the adventitia of the bifurcation. Another consideration in the mobilization of the carotid bifurcation is the possibility of permanent injury to the carotid sinus nerve and injury to the carotid body, which may have some significance if bilateral loss occurs. Temporary loss of normal compensatory responses to hypoxia may occur in bilateral carotid body injury following carotid endarterectomy.[14] Furthermore, an increase in blood pressure may result from bilateral carotid sinus denervation. Hickey et al.[14] reported a 26% increase in the systolic pressure and a 30% increase in diastolic pressure in a series of patients following bilateral carotid endarterectomy.

Common carotid–subclavian bypass. The second most common operation for extracranial arterial obstruction in my experience is common carotid–subclavian bypass for an occluded subclavian artery. This procedure may be combined with carotid endarterectomy on the same side. This operation does not result in a "steal" from the cerebral circulation unless a significant stenosis is present in the common carotid artery proximal to the shunt.[5] The preponderance of flow through the common carotid artery to either the distal common carotid or to the subclavian artery via the bypass depends on the vascular resistance in each of those systems supplied.

The surgical approach for common carotid–subclavian bypass is illustrated in Fig. 14-9. The subclavian artery is approached by a transverse supraclavicular

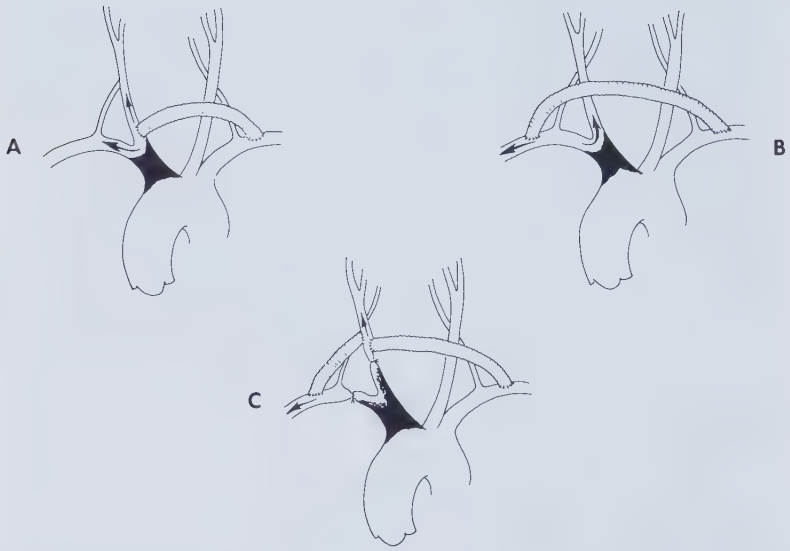

Fig. 14-10. Extrathoracic bypass procedures for innominate artery occlusion. **A,** Left subclavian-right common carotid bypass. **B,** Left subclavian-right subclavian bypass. **C,** In instances where occlusive process extends into bifurcation, bypass to right common carotid artery with bypass to right subclavian artery may be preferable. Origins of common carotid and right subclavian arteries can then be ligated to prevent possible embolization of arteriosclerotic material at bifurcation.

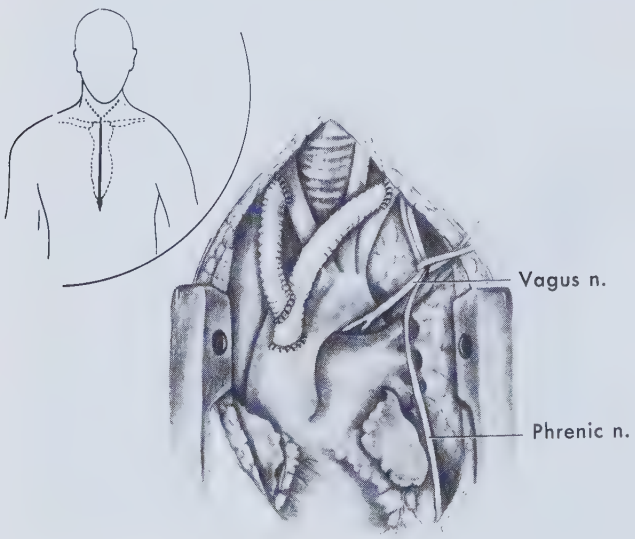

Fig. 14-11. Surgical approach for bypass from ascending aorta to innominate, carotid, or subclavian arteries.

incision dividing the sternocleidomastoid and anterior scalene muscles. Either an 8 mm Dacron graft or an autogenous vein graft may be used. The subclavian anastomosis is performed before the carotid anastomosis.

Other bypass procedures. Subclavian–common carotid bypass may be performed for occlusion of the common carotid artery using the same technique just mentioned. Subclavian-subclavian bypass may also be performed for occlusion of one subclavian artery. Extrathoracic approaches for innominate artery occlusion include left subclavian–right carotid bypass or left subclavian–right subclavian bypass (Fig. 14-10, *A* and *B*). A theoretic advantage to the former technique is that flow may be better directed into the common carotid artery, although peripheral resistance is the major determinant of distal flow. A second advantage is that flow to the carotid artery does not have to bypass a bifurcation where arteriosclerotic plaque and thrombus are situated. If the occlusion extends into the bifurcation of the innominate artery, separate limbs to the right subclavian and right common carotid arteries are preferred, and the pressure of thrombus material would be an indication for ligation of the common carotid and subclavian arteries at their origins (Fig. 14-10, *C*).

In good-risk patients with innominate artery occlusion or multiple occlusions of the origins of the carotid or subclavian arteries, operation is often performed through a median sternotomy with the bypass constructed from the ascending aorta (Fig. 14-11).

Vertebral artery stenosis is an uncommon indication for operation in my experience. The exposure is illustrated in Fig. 14-9. Patch repair is often preferred to endarterectomy.

Results

The most frequent operation for extracranial cerebral arterial insufficiency is carotid endarterectomy in patients with transient cerebral ischemia. My experience and that of others indicates that the operative mortality is approximately 1% or less and that the incidence of stroke as a result of operation performed in patients without a neurologic deficit is less than 1%.[25, 26]

Results of the *Joint Study of Extracranial Arterial Occlusion* demonstrated a significant decrease in transient ischemic attacks among patients having carotid endarterectomy, as compared to a similar group of patients not operated on ($p = 0.0001$).[9] Thompson et al.[25] reported that among patients who had carotid endarterectomy for transient cerebral ischemia and who were followed up for 6 months to 13 years, 81% were asymptomatic and 15.7% showed improvement. Among 293 patients operated on for transient cerebral symptoms, 79 patients died during the follow-up period; 52.3% of the deaths were due to cardiac disease and only 13.4% resulted from stroke. Wylie and Ehrenfeld[26] reported an incidence of new transient ischemic attacks of 5% among 247 patients after carotid endarterectomy for transient ischemia and followed up for an average of 4 years. The incidence of subsequent stroke among those patients was 6.5%; 2.5% of patients died from stroke and 12.6% died from other causes.

Among patients with completed stroke who had carotid endarterectomy, Thompson et al.[25] observed that 30.2% were asymptomatic and 58.7% showed improvement during long-term evaluation.[25] The results of Wylie and Ehrenfeld[26] also suggest that appropriate carotid endarterectomy in patients with stable com-

pleted stroke reduces the probability of a second stroke.[26] Three of 112 such patients experienced a new stroke during an average follow-up period of 4 years.

My results as well as those of others include no deaths as a result of carotid endarterectomy in patients with asymptomatic carotid stenosis.[25, 26] Follow-up in such patients suggests that the risk of stroke is reduced when compared to asymptomatic patients with carotid stenosis not operated on.

Extrathoracic bypass procedures for obstructions of the innominate, common carotid, and subclavian arteries have been employed with increasing frequency. Crawford et al.[4] reported a mortality of less than 4% in patients with obstructions of the innominate, common carotid, and subclavian arteries when extrathoracic bypass procedures were used in a majority of instances. My experience is in agreement with others that over 90% of patients with bypass procedures of the innominate, common carotid, or subclavian arteries are subsequently either asymptomatic or show improvement.[4, 26]

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15

Intraoperative autotransfusion

JAMES B. DOWLING

Intraoperative autotransfusion is the salvage of blood and blood components from the operative field and their filtration and reinfusion into the patient. The concept of autotransfusion was first proposed in the nineteenth century by Highmore,[13] who suggested the reinfusion of blood lost from a patient with postpartum hemorrhage. Although he did not employ the technique, his suggestion of reinfusing the blood appeared in an article he published in 1874.

The first reports of autotransfusion in the United States appeared in 1917, when Lockwood reported recovering and reinfusing 750 ml of blood in a patient undergoing splenectomy for Banti's disease.[28] Cushing in 1925 reported autologous blood replacement performed during 25 selected neurosurgical procedures. In 1943 Griswold and Ortner[12] reported the use of autotransfusion in abdominal and thoracic trauma. Their series comprised 100 patients in whom the mortality was 30%, much lower than the expected mortality in a group of patients with equivalent blood loss. One death in their series was directly attributable to the use of the system. This involved the aspiration of blood and fecal particles from a patient with an open colon injury and the subsequent infusion of the contaminated material into the patient.

The further development of autotransfusion was neglected in the late 1930's. This neglect was directly attributable to the advent of the large-scale use of donor blood transfusions.[28] The first blood bank in the United States was established at the Mayo Clinic in 1935.[29] With the development of techniques of storing, preserving, and screening donor blood, its use became widespread over the next 25 years.

During the last 20 years the dangerous sequelae of banked blood transfusions have become readily apparent, with the most common complication being febrile or allergic responses. The transmission of viral disease, circulatory overload, and hemolytic reactions are not infrequent serious complications of blood bank transfusions.[1, 2, 5, 14]

It is estimated that each year 30,000 patients in the United States develop posttransfusion hepatitis with an annual mortality of 4000. Approximately 1 in 200 donors is a carrier of the hepatitis virus.

The cost of staffing a blood bank, recruiting donors, and collecting, processing, storing, and shipping blood has quadrupled in the last 10 years. This fact, coupled with the waste of blood bank blood each year, brings the economic aspects of the problem to the forefront. In 1966, 5.2 million units of blood were collected with 3.4 million transfusions given and 1.8 million units discarded because they were outdated, an estimated loss of $18 million.[29]

In the last 20 years with the marked increase in trauma, advances in cardiovascular surgery, and new techniques in extensive cancer surgery, the demand for blood and blood products has markedly increased. The increased demand has created relative shortages of blood and blood products in most communities.

The complications of blood bank transfusions, the cost of collecting, processing, and distributing blood products, and the increased demand and short supply have rekindled interest in establishing safe and economically feasible alternatives to alleviate these problems.

Many techniques of autotransfusion have been formulated. Cuello et al.[8] reported a series of 67 patients undergoing elective surgical procedures who were phlebotomized preoperatively and autotransfused intraoperatively or in the immediate postoperative period. This technique has enjoyed limited clinical success but has obvious limitations. The trauma patient or the debilitated patient undergoing extensive surgical procedures would not qualify for this method of autotransfusion.

The advances in techniques of open-heart surgery with the use of cardiac bypass procedures has stimulated the development of blood filters capable of filtering particulate matter with minimal damage to the cellular elements of blood. Klebanoff[15] and Klebanoff et al.[17] reported a limited clinical trial of intraoperative autotransfusion using a prototype of the Bentley Cardiometry Reservoir with a 125 micropore filter. He aspirated the blood from the operative site, filtered it, and then reinfused it into the patient during the operative procedure. Employing a similar technique, Symbas[27] reported clinical and laboratory studies in patients with hemothorax. In the 150 patients studied the mean volume autotransfused was 1500 ml, with no serious complications resulting. Both of these studies pointed out that autotransfusion was restricted in clinical use as only a lifesaving measure.

Recent advances in the production of synthetic, disposable materials at relatively low cost have overcome the economic hurdle to the widespread use of autotransfusion. Many of the methods employed up until recently have been limited in their application by the excessively high cost of production to a very limited clientele. The autotransfusion devices now being marketed require a relatively small initial investment and have consequently enjoyed more widespread acceptance by the clinician and researcher.

Based on the work of Klebanoff, Symbas, and other pioneers in the field, recent limited clinical trials have been undertaken at medical centers across the country. Initial results of these experiences have met with a modicum of success; however, many nagging questions remain unanswered. The technique of anticoagulation in employing the unit has been quite controversial and is as yet not

fully developed. The problems of possible aspiration and reinfusion of particulate matter, the incidence of posttraumatic pulmonary insufficiency, the possibility of renal damage, the incidence of disseminated intravascular coagulopathy have all been met with encouraging results. The potential dangers of air embolus and pressurized infusion have been overcome by improved safety mechanisms built into the unit. From reports of the early clinical experience with intraoperative autotransfusion, it has become apparent that proper use of the system can be a valuable adjunct to the clinician in selected patients.

INDICATIONS

A 2500-bed metropolitian hospital with a large trauma service and a chronic shortage of blood is a thumbnail insight into why the Tulane Surgical Service at Charity Hospital became interested in an autotransfusion system. The prospect of preserving the limited blood resources for major elective procedures by using an autotransfusion system became quite appealing. It was anticipated that such a system would be of real practical value in an institution such as Charity Hospital. It was believed that employing such a system in the trauma procedures would substantially alleviate a major drain on the blood bank resources.

The indications for the use of the system are as follows: (1) trauma with exsanguinating hemorrhage, (2) extensive surgery, (3) inability to obtain blood, (4) unusual blood type, (5) previous transfusion reaction, (6) bleeding diathesis, and (7) religious beliefs.

The first consideration is the trauma patient with exsanguinating hemorrhage. The hallmark in the successful treatment of trauma is the speed with which hemostasis is obtained, along with adequate replacement of blood volume. In using the system the 45 min delay in cross matching whole blood was circumvented and the patient was not subjected to the serious sequela of administering uncross-matched whole blood. For the patient undergoing elective surgery the use of the autotransfuser is of value in protecting the patient against sudden unexpected blood loss and in retrieving blood during the procedure that may be readministered to the patient if needed. Unusual blood type and inability to obtain blood are frequent causes for delay in scheduling elective procedures. This delay can be eradicated by the use of an autotransfusion system.

Previous transfusion reaction assumes little clinical importance, since the patient's own blood is retrieved, filtered, and reinfused.[15] Patients with bleeding diathesis would be ideal candidates for the use of the system. The rapid replacement of an unexpected heavy blood loss with the patient's own fresh blood will be a valuable aid in elective surgical procedures. Finally, those people whose religious beliefs forbid homologous blood transfusion are in most cases agreeable to the reinfusion of their own blood.

ADVANTAGES

Taking into consideration the indications for autotransfusion, the advantages of the system become readily apparent. The rapid replacement of blood retrieved from the operative site creates in essence a partial bypass system. The ability to deliver large quantities of blood or volume expanders enables the surgeon to replace volume deficits created and to maintain an adequate intravascular volume during the operative procedure. Maintaining an adequate intravascular volume

during any procedure on the severely injured individual is a major advance in traumatic surgery. It assures the surgeon of adequate perfusion of uninvolved viscera during the operation and will prevent many of the serious sequela of prolonged hypovolemia. The ready availability of fresh, compatible blood will eradicate needless delays prior to surgery. With improved preservation of labile clotting factors in fresh, compatible blood, I would hope to see a decrease in the incidence of disseminated intravascular coagulation, which has become a real nemesis in all major trauma centers.

The last major advantage of the system is the prevention of the sequelae of standard transfusion techniques, i.e., hepatitis and blood reactions. Blood banks have certainly made tremendous strides in the past decade with new and very sophisticated screening techniques in attempting to overcome these problems. However, it remains that there are 4000 deaths in the United States per annum directly attributable to homologous blood transfusion.[29] It is hoped that the more widespread use of autotransfusion will significantly reduce this statistic.

MATERIAL AND METHODS

Fig. 15-1 is a photograph of the autotransfusion unit presently employed by the trauma service at Charity Hospital. The basic system of this particular model* is made up of two major components. The first is a permanent two roller–head pump with speed control over a range of 0 to 150 rpm; maximum flow rate for providing suction is approximately 3500 ml/min. Also included in the pump is a pressure control system. The pressurized infusion of blood from the reservoir may be accomplished easily and safely by depressing the pressure infusion level. The maximum pressure that can be applied through rapid infusion is automatically limited by the pressure-regulating mechanisms. The pressure infusion control includes a dial that makes possible adjustments of the maximum infusion pressure over a range of 50 to 250 mm Hg. Also included in the unit is a color-sensitive photoelectric cell that will sound an alarm when the level of fluid in the reservoir falls below 200 ml.

The second major component of the system is disposable sterile prepackaging tubing and a reservoir. The suction line leads into the base of the reservoir and filtering system, and the two effluent lines then lead to the patient. The entire system placed on a cart is very mobile and can be assembled and ready for use in less than 5 min.

Since the experience of the trauma service at Charity Hospital has been exclusively with the trauma patient, a few modifications have been made in the system to better adapt it to these particular needs. Each patient had a central venous pressure (CVP) monitoring device inserted prior to going to surgery. Our preference is to cut down the external jugular vein and to insert a no. 8 infant feeding tube. This allows not only for CVP monitoring but also for administration of up to 1500 ml/min if the need arises.

Another advantage of this method is the ability to suture the cannula under direct vision, ensuring its stability if the need arises to infuse under pressure. Subclavian catheterization has not been employed for any patients receiving autotransfusion on the trauma service. The blind cannulization of the subclavian

*Bentley Laboratories, Irvine, Calif.

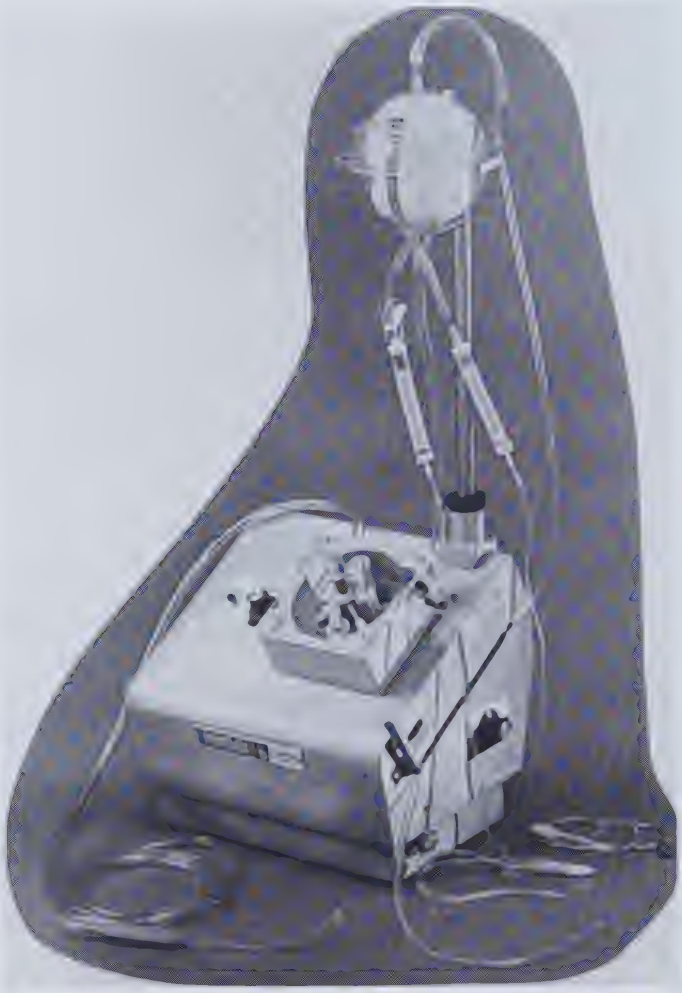

Fig. 15-1. The Bentley ATS 100 assembled and ready for use. The disposable reservoir and tubing are sterilized and prepackaged.

vein and the inability to secure the catheter to the vessel preclude the use of any pressurized infusion.

Priming of the pump and reservoir was accomplished by using 500 ml of Ringer's lactate solution. We found this volume to be ideal in initiating a safe fluid level in the reservoir and in priming both lines leading to the patient. Anticoagulation of the priming solution has been a controversial topic. There are three basic methods used for anticoagulation—total systemic heparinization, partial heparinization, or the use of ACD.[7-11] The method used in our series was partial heparinization by adding a predetermined amount of heparin to the priming solution. Since all the patients were trauma patients and the vast majority had multisystem injuries, it was believed that this precluded the use of total heparinization.

With the advent of cardiopulmonary bypass, there have been many refine-

ments made of the types of suction tips employed. The coronary suction tip has been shown in studies by cardiovascular surgeons to inflict the least damage on the erythrocytes. Based on these studies and the knowledge that the blood would be filtered under pressure, the preference at this time is to use the coronary suction tip with the autotransfusion system.

The disposable component of the unit was changed after the autotransfusion of 2500 ml, the equivalent of 5 units of whole blood. Since 90% of the patients were infused under pressure, it was found that the filtering system became obstructed with clot and particulate matter, markedly reducing the efficiency of the system if more than 2500 ml was infused under pressure.

Posttraumatic pulmonary insufficiency has become well recognized in the last few years as a serious sequela to massive transfusions, a presumed etiologic factor being precipitated particulate matter in the transfused blood.[21] The trauma service at Charity Hospital has employed commercially available filters* in the effluent lines going to the patient; it was found that this did not drastically reduce the efficiency of the system, and significant amounts of particulate matter were filtered out.

CLINICAL EXPERIENCE

The total number of patients included in this series is 74. The data for this presentation was collected over a 12-month period through September 1, 1973. The age range of the patients included in this series was from 16 to 64 years of age, and the mean age was 32 years of age. The race distribution was 43 Negros and 31 Caucasians. The spectrums of age, sex, and race in the series are fairly characteristic of a major trauma service. There were 10 deaths in the series. Five of the deaths were intraoperative, and five were in the postoperative period, the overall mortality rate being 13.4%. Of the intraoperative deaths, three were caused by the severity of the injuries received, one was due to disseminated intravascular coagulopathy, and one resulted from air embolus. Of the postoperative deaths, three were due to concomitant severe head injuries, one was due to a pulmonary embolus 18 days postoperatively, and one patient died 48 hr after surgery, having developed disseminated intravascular coagulation during a prolonged period of hypotension.

The patient with an air embolism is the only fatality in this series directly attributable to the use of the system. The patient was a 29-year-old male who sustained a stab wound to the left chest with transection of the subclavian artery and vein. As the vessels were being isolated, a sudden rush of air was noted in the vein. The patient fibrillated and developed asystole, refractive to open-chest massage and other resuscitative measures. The errors in this case were both human and mechanical. It is of the utmost importance to maintain a fluid level in the reservoir of at least 200 ml, especially when infusing under pressure as was being done in this particular case. The attendant operating the system looked at the reservoir and mistook a clot and stain on the filter for a fluid level. He then turned his attention to the operative field for a few moments, only to see the rush of air.

The mechanical failure was the failure of the alarm triggered by the photo-

*Size 20 to 40 micropore Swank Filter manufactured by Pioneer Filter, Inc., Hillsboro, Oregon.

electric cell to warn that the fluid level was dangerously low. The photoelectric cell is color sensitive. Obviously the clot and stain on the filter was all that was needed to keep the alarm silent.

The air embolus occurred early in the series and since that time a number of steps have been taken to protect against its recurrence. The first step is that a trained technician is employed whose sole responsibility during the procedure is the operation of the autotransfusion unit. To expect the surgeon or the anesthesiologist to operate the autotransfusion system during emergency procedures is inviting catastrophe. Second, on patients with exsanguinating hemorrhage two autotransfusion units are employed when possible. The units are used intermittently, aspirated blood filling the reservoir in one unit and then being reinfused into the patient while aspiration continues with the second unit.

Bentley Laboratories has also made modifications in the original prototype to better protect against the possibility of air embolism. First, the size of the reservoir has been increased, obtaining a safe fluid level in the new enlarged reservoir in the range of 400 to 600 ml. Second, improvements have been made in the photoelectric cell, making it sensitive to a fluid level as well as color sensitive.

Fifty-two of the 74 patients (70%) sustained a major vascular injury. Only 16 patients (21%) of the series sustained an isolated vascular injury with exsanguinating hemorrhage. Multiple system injuries occurred in 79% of the patients included in this series.

The mean volume autotransfused among the 74 patients was 1840 ml/patient or the equivalent of 3½ units of whole blood. The range of autotransfusion in the series varied from 350 ml in a patient with an isolated hemotherax to 12,500 ml in a patient with multiple vascular injuries. Measurements of the amount autotransfused was determined by using the system intermittently, filling the caliberated reservoir with a known amount and subtracting the amount of priming solution.

Fifty-four of the 74 patients in the series also received homologous whole blood in addition to the autotransfused blood. The range in these 54 patients was from 250 ml to 45 units of whole blood, the mean being 800 ml/patient. When Swank filters were utilized, the homologous whole blood was administered through the same lines as the autotransfused blood.

COMPLICATIONS

The presence of hemoglobinuria and elevated levels of plasma-free hemoglobin were the most common alterations encountered after employing the autotransfuser. Hemoglobinuria was present in all patients receiving more than 750 ml of autotransfused blood. In all cases this phenomenon was transient, usually clearing within 24 to 48 hr. There were no cases of acute tubular necrosis or renal failure in the surviving patients. Elevated plasma-free hemoglobin levels were demonstrable in all patients receiving over 500 ml of autotransfused blood. This phenomenon was also transient, with plasma-free hemoglobin levels returning to normal levels within 24 hr. The high incidence of hemoglobinuria and elevated levels of plasma-free hemoglobin were attributed to the fact that the system was pressurized when in use with the vast majority of patients. Forcing

the erythrocytes through the filtering system under pressure contributed to the destruction of a proportion of cells.

Disseminated intravascular coagulopathy was clinically suspected and documented by hematologic screening in six patients. All patients who were autotransfused with more than 1500 ml of blood were screened for evidence of clotting deficiencies. In each patient with documented disseminated intravascular coagulopathy, significant amounts of homologous cross-matched or uncross-matched whole blood had been administered. There were no cases of disseminated intravascular coagulopathy in which the patient received exclusively autotransfused blood.

Posttraumatic pulmonary insufficiency was demonstrated in six patients during the postoperative period. Four of the six patients received significant amounts of homologous whole blood prior to employing the autotransfusion system. The other two patients had significant thoracic injuries and pulmonary contusions. Posttraumatic pulmonary insufficiency is mentioned because of the possibility that particulate matter being autotransfused was an etiologic agent.[29] Results of the reported series fail to substantiate this, since the patients received either significant amounts of homologous whole blood or had concomitant thoracic injuries. Posttraumatic pulmonary insufficiency was not encountered, and those patients who were autotransfused did not receive homologous whole blood.

In six of the 74 patients included in this series, the autotransfuser was employed in the presence of open colon injury. The indication for use of the system was as a lifesaving measure in the presence of exsanguinating hemorrhage. Blood cultures during the procedure and in the postoperative period were negative. Not one of these patients developed clinical sepsis. We are certainly not advocating the use of the autotransfusion system in patients with grossly contaminated wounds; however, in the presence of exsanguinating hemorrhage from major vascular injury we have found the system to be a tremendous aid. In all of the contaminated patients the source of contamination was isolated from the operative field with laparotomy pads. The operative field was kept free of any further gross contamination. Autotransfusion was then employed, hemostasis obtained, and the injury repaired. Based on our experience and the laboratory studies by Klebanoff et al.[16] concerning contaminated wounds, we do not feel that the contaminated wound automatically precludes the use of the autotransfusion system.

Dangerously low fibrinogen levels were measured in 18 of the 74 patients. Included in these 18 patients were the six with documented disseminated intravascular coagulopathy. There was no correlation between the amount of blood autotransfused and the lowest serum fibrinogen levels. It appeared that in the 18 patients with low serum levels prolonged periods of pooling of blood prior to aspiration and reinfusion were associated with a decrease in serum fibrinogen levels. This encouraged the belief that the time of tissue contact was the determining factor in activating fibrinolytic activity. Twelve of the 18 patients with serum levels that measured as low as 50 mg% in the immediate postoperative period experienced a return to normal levels within 36 hr after the operation.

Low platelet counts were encountered in patients who had prolonged pooling of the blood in tissue contact and in patients for whom the reservoir and filter

were not changed at regular intervals. This is attributed to the prolonged tissue contact and activation of factors influencing platelet aggregation both at the tissue level and in the reservoir. Fresh platelet packs were administered to 10 patients in whom the immediate postoperative count was below 50,000 platelets/mm^3.

All patients being autotransfused were monitored intraoperatively and checked every 12 hr up to 72 hr after the operation by evaluating blood and urine parameters, complete blood cell count, blood urea nitrogen, plasma hemoglobin, serum fibrinogen, prothrombin time, platelet count, partial thromboplastin time, and urine specific gravity.

Figs. 15-2 to 15-6 demonstrate the alterations observed in the aforementioned parameters in a patient massively autotransfused. This particular patient was a victim of the Howard Johnson sniper incident in January 1973. The patient

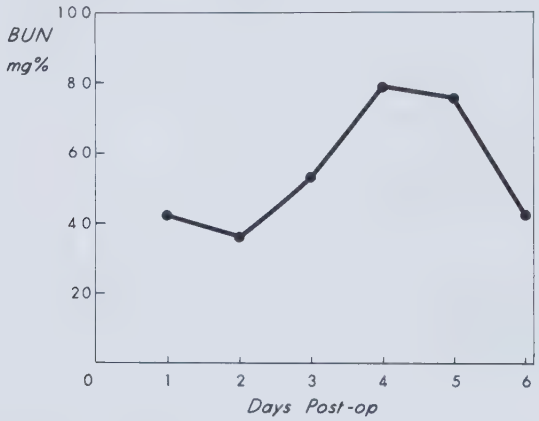

Fig. 15-2. Serial blood urea nitrogen levels in a patient autotransfused with 4500 ml blood.

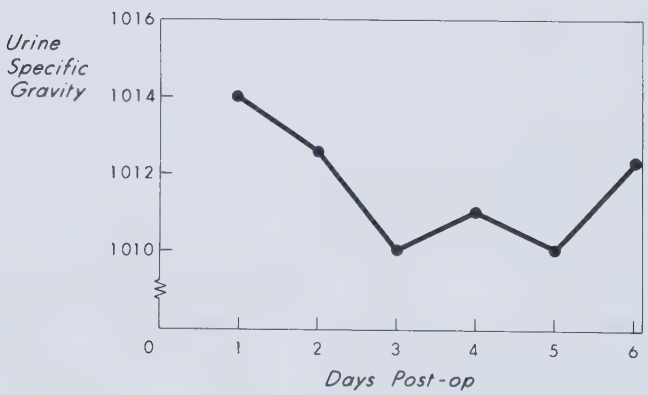

Fig. 15-3. Serial measurement of urine specific gravity in patient with extensive soft tissue injury who was autotransfused. Patient's blood urea nitrogen levels plotted in Fig. 15-2. Patient showed evidence of high-output renal failure on postoperative days 2 through 6. Cell parameters of renal function returned to normal by 10 days postoperatively.

was a 56-year-old male who sustained a 440-magnum gunshot wound to the left flank from a distance of 10 feet. Approximately 25 min later he arrived at Charity Hospital with a blood pressure of 50/0 mm Hg and a pulse of 140. There was a large gaping entrance wound in the left flank with evisceration of abdominal contents. There was no exit wound but a large hematoma of the anterior abdominal wall. He was given 4 L of Ringer's lactate via two central venuos catheter cut-downs. Intravenous pyelogram demonstrated extravasation from the left kidney; the chest x-ray film was unremarkable. The patient arrived in surgery 40 min after injury. Through an anterior midline incision the following injuries were found: perforations of the aorta, vena cava, left iliac artery and vein, small bowel, left colon, left kidney and ureter, and vertebral bodies and complete obliteration of the left retroperitoneal space. During the ensuing 5 hr operative procedure, the aforementioned injuries were repaired. During the entire pro-

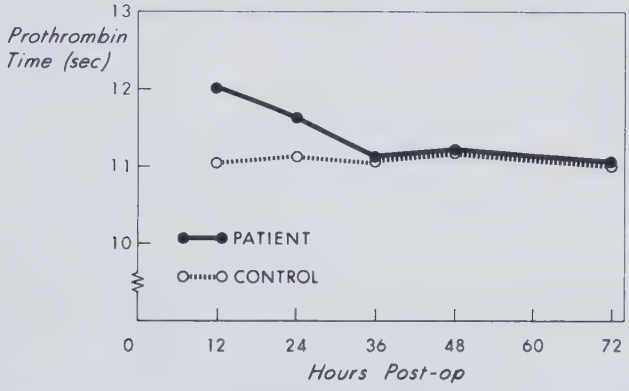

Fig. 15-4. Slight prolongation of prothrombin time, returning to normal within 24 hr in patient autotransfused with 9 units of blood.

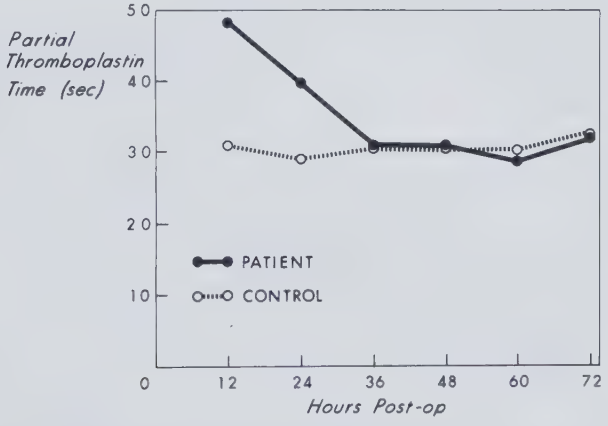

Fig. 15-5. Partial thromboplastin curve of patient referred to in Fig. 15-4. Patient also received 20 units of homologous whole blood administered via autotransfusion system. Clotting abnormalities in this patient returned to normal by 3 days postoperatively.

cedure the patient remained hypotensive, with the blood pressure ranging from 0 to 70 mm Hg systolic. For 45 min of the operation he had no obtainable blood pressure. The autotransfusion system was used throughout the procedure. Intraoperatively he received 11 L of Ringer's lactate, saline solution, and D_5W and normal saline solution plus 45 units homologous whole blood.

The system was primed with 500 ml Ringer's lactate to which was added 3000 units of aqueous heparin. The open visceral injuries were isolated from

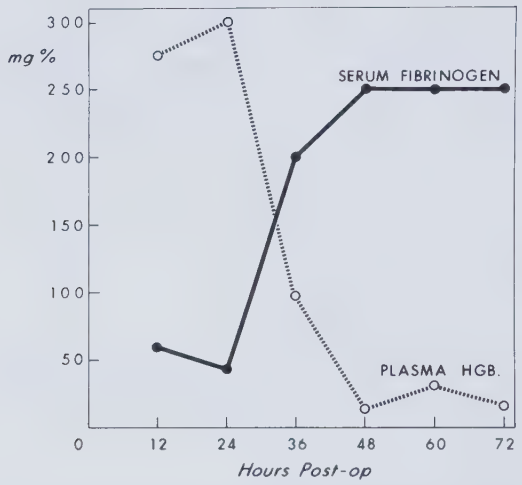

Fig. 15-6. Marked elevation of plasma hemoglobin seen in patient autotransfused with 5500 ml blood. Elevations in plasma hemoglobin were seen in all patients autotransfused with more than 500 ml. Elevations were transient, usually clearing within 48 hr. Marked decrease in serum fibrinogen levels in this patient is also demonstrated, again returning to acceptable levels by 72 hr postoperatively.

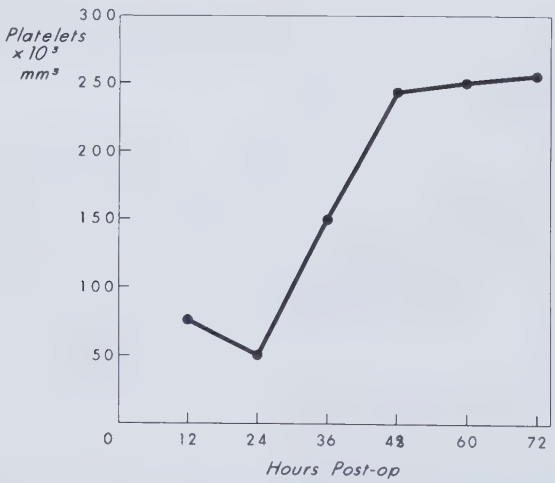

Fig. 15-7. Patient referred to in Fig. 15-6 showing dangerously low platelet counts 24 hr postoperatively. Patient did not develop bleeding diathesis and was given fresh frozen platelets with a return to acceptable levels by 3 days postoperatively.

the operative field and the unit was employed. During the procedure the disposable unit of the system was changed six times. The total heparin dose over the 5 hr was 12,000 units. The total amount of fluid administered via the autotransfusion system was 45 units of whole blood, 11 L of volume expanders, and an estimated 12,500 ml of aspirated and autotransfused blood.

The patient received 75 Gm of mannitol in divided doses, and 400 mg of furosemide (Lasix) in 500 ml D_5W was administered over a 6 hr period in an attempt to maintain adequate renal function during the prolonged period of hypotension.[3, 4, 18, 19, 23, 25] Figs. 15-2 and 15-3 demonstrate the urine parameters followed during this patient's postoperative course. On the third postoperative day the patient's renal function began to deteriorate and he showed signs of high-output renal failure. His blood urea nitrogen and serum creatinine levels rose, his output increased from 1500 to 3200 ml over a 24 hr period, and his urine concentration fell off on days 3 to 5. By the tenth postoperative day the patient had a normal creatinine clearance, normal blood urea nitrogen, and his urine specific gravity had returned to normal levels with no further evidence of renal dysfunction.

Figs. 15-4 and 15-5 demonstrate alterations in the patient's serum prothrombin time and partial thromboplastin time in his first 72 hr after the operation. The slight prolongation of the prothrombin time had returned to normal by 36 hr after the operation; also, the serum partial thromboplastin time had returned to within normal limits in the same time interval. Fig. 15-6 demonstrates the marked elevation of plasma-free hemoglobin in the serum in the immediate postoperative period up to levels of 300 mg% within 24 hr of operation. During the first 3 postoperative days the patient had hemoglobinuria, but it cleared 48 hr after the operation. At this time his plasma-free hemoglobin levels had also returned to more acceptable limits. Also demonstrated in Fig. 15-6 are the dangerously low levels of serum fibrinogen, less 50 mg% within 24 hr after the operation. These were attributed to the massive amount of homologous whole blood and autotransfused blood the patient had received in his first 12 hr in the hospital. Serum fibrinogen levels had returned to normal limits within 48 hr after the operation. The patient's platelet count dropped to 46,000/mm^3 in the first 24 hr, the patient was transfused with two fresh frozen platelet packs, and he had acceptable platelet counts by 48 hr after the operation (Fig. 15-7).

SUMMARY

This chapter has presented the clinical experiences at Charity Hospital with intraoperative autotransfusion. During the 12 months of the study the autotransfusion technique was employed with 74 trauma patients. Its use, as demonstrated by the illustrative case, is an invaluable adjunct in trauma surgery. The particular patient whose case was presented would not have survived the operative procedure had the system not been used. The ability to maintain an adequate circulating intravascular volume and therefore tissue profusion until repairs can be performed and hemostasis is obtained is an advantage of the system that cannot be stressed enough. As the reported experience has indicated, the use of the autotransfuser has been a valuable asset in the following areas:

1. Maintaining an adequate intravascular volume in the trauma patient
2. Preventing unnecessary delay to definitive surgery

3. Making ready available fresh compatible whole blood
4. Preventing the depletion of blood bank resources
5. Removing the obstacle of serious sequelae to standard transfusion techniques

If properly employed, the autotransfusion system will become a necessary and valuable asset to any major trauma service.

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16

Anaerobic infections

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The distinct clinical syndromes of gas gangrene, tetanus, and botulism produced by clostridia are familiar to all clinicians. However, these entities are much less common than the infections due to the nonspore-forming anaerobic organisms that cause a wide variety of clinical infections such as bacteremia, peritonitis, empyema, wound infections, and abscesses. Although anaerobes in large numbers have been recognized as commensals of man for many years, it is only recently that the medical literature has discussed with increasing frequency the importance of clinical infections caused by these organisms. Most of the anaerobic infections, especially those due to *Bacteroides*, occur in surgical patients, yet there has been little emphasis on these infections either in surgical teaching or in the surgical literature.[7]

The recent improvements in anaerobic culture techniques have facilitated identification of these organisms and emphasized their contribution to surgical infections.[26] Still there is a lack of recognition for anaerobic infections as manifested by the paucity of requests for anaerobic cultures, the improper methods of obtaining and transporting clinical specimens, and the poor choice of antibiotics when there is a high index of suspicion for an anaerobic infection.

Anaerobes were probably the first forms of life on earth at a time when the atmosphere lacked oxygen and was composed primarily of methane, hydrogen, and ammonia. Even with the advent of oxygen production the anaerobes have persisted, either in circumstances where oxygen could not penetrate or where oxygen was consumed by aerobic organisms or oxidative enzymes. Anaerobes are indeed ubiquitous organisms that are present in decaying vegetation, in the soil, and on the bodies of animals. These bacteria are extremely common and exist in the mouth, the skin, the female genital tract, and the intestines. In

the oral cavity, aerobes and anaerobes exist in equal numbers; on the skin, the vagina, and the colon, the anaerobes far outnumber the aerobes.[30]

Not only are the nonpathogenic anaerobes present on the body, but almost all the pathogenic anaerobic bacteria exist there as well. As a result, three considerations pertain: (1) there must be a modification of the existing conditions in order to permit the potential pathogenicity to be manifested; (2) most of the infections with anaerobes are endogenous in origin; and (3) because of their ubiquitous nature, anaerobes that are present on cultures of infections may not necessarily be significant.

There exists a spectrum of anaerobes from those able to grow under low oxygen tension in the presence of carbon dioxide to the most fastidious anaerobes that require the complete absence of oxygen. *Facultative anaerobes* are able to live under either anaerobic or aerobic conditions. Many of the frequently encountered, clinically significant aerobic bacteria have the ability to grow anaerobically and must be distinguished on culture from the true anaerobic organisms. *Microaerophilic* organisms can grow under reduced oxygen tension or under aerobic conditions in the presence of 10% carbon dioxide. *Aerotolerant* organisms can grow feebly aerobically, especially after an initial culture under anaerobic conditions. However, it is to the *obligate anaerobes* that can grow only in the complete absence of oxygen that this discussion is primarily directed.

The presence of anaerobic microorganisms has been recognized for a little more than 100 years, since Pasteur became aware that the microbes that produced butyric acid *(Clostridium butyricum)* were immobile when exposed to air but mobile when the air was removed. Human anaerobic infections were first described in 1897 by Veillon and Zuber.[38] Since then there has been gradual but persistent development of this field. It was previously estimated that from 4% to 10.5% of all human infections were anaerobic in origin. More recent studies have demonstrated anaerobic organisms in one third of postoperative wound infections[19] and two thirds of intra-abdominal abscesses.[3] At the Mayo Clinic in 1968, 39.5% of 820 positive cultures contained anaerobic bacteria.[41] There are a few relatively recent reviews of anaerobic infections[8, 14, 16, 26, 34]; none of these have appeared in the surgical literature.

ANAEROBES OF CLINICAL SIGNIFICANCE

The nomenclature of anaerobic microorganisms used in the literature varies significantly depending on the author and the date of the article. Frequently the generic names given to well-defined species are not the same in different classification systems. Many of the generic names of anaerobic bacteria used in this chapter are those listed in the seventh edition of *Bergey's Manual of Determinative Bacteriology*[9] and have been patterned largely after the system used by Prevót at the Pasteur Institute in Paris.[29] However, the rapid advances in the classification of anaerobes have resulted in the new terminology that is used in this discussion, when appropriate.

The classification of anaerobes may appear confusing because of the large numbers of anaerobic bacteria, the constant identification of new types, the inability to speciate 82% despite the use of sophisticated techniques,[26] and the continuous reclassification of organisms into new genera and species.[14] Fortu-

nately it is possible to condense the clinically significant anaerobes into the following shortened and simplified list to facilitate discussion of the subject.

Sporulating bacilli
Clostridium
Gram-negative bacilli
Bacteroides
Fusobacterium
Gram-positive cocci
Peptococcus (anaerobic staphylococcus)
Peptostreptococcus (anaerobic streptococcus)
Gram-positive bacilli
Actinomyces (fungus)
Propionibacterium (anaerobic diphtheroids)
Gram-negative cocci
Veillonella

The ability of anaerobes to cause infection is variable. Many are not pathogenic for man, and some are only recovered as contaminants. The clinical significance of a large number of anaerobes is often unclear because they exist only with other organisms and not in pure culture and because they do not lead to infections when injected into animals. Most of the gram-negative nonspore-forming rods, exclusive of *Bacteroides* and *Fusobacterium,* fall into this category. Similarly, the gram-positive nonspore-forming rods, exclusive of *Actinomyces israelii,* may be similarly described. However, it is important to recognize that in both these groups almost all organisms have on rare occasions been isolated in pure form from clinical material, which is at least circumstantial evidence that they can be pathogenic.[34] Certain anaerobes are clearly pathogenic with well-defined syndromes (tetanus, botulism, clostridial myonecrosis, etc.) or with general infectious processes (abdominal abscesses and septicemia associated with *Bacteroides*).

Sporulating bacilli

Clostridium. Of all the anaerobic bacteria, the characteristics, classification, and pathogenic properties of the clostridia are best understood. They are the only spore-forming anaerobic organisms, and identification of an anaerobe as *Clostridium* depends on demonstration of spores, which can be difficult in the case of *C. perfringens* and *C. ramosum. C. perfringens* is the most common pathogenic species, and unlike other clostridia does not produce spores in tissues. Although most of the clostridia are obligate anaerobes, two species, *C. tertium* and *C. histolyticum,* can grow aerobically. Of close to 100 different species of clostridia, less than a dozen are associated with human disease.[8] Tetanus produced by *C. tetani* and botulism caused by *C. botulinum* are more properly described as intoxications rather than infections. In addition to *C. perfringens,* the less common *C. novyi* and *C. septicum* and the still rarer *C. histolyticum, C. bifermentans,* and *C. fallax* are all capable of causing myonecrosis (gas gangrene), anaerobic cellulitis, septic abortions, and operative wound infections. Clostridia are found as part of the normal bowel flora, in the soil, and irregularly in the mouth and female genital tract. However, *C. tetani* is rarely recovered from human feces (1.5%), and thus tetanus is probably infrequently endogenous in origin.[39]

Gram-negative bacilli

Bacteroides and Fusobacterium. Bacteroides and *Fusobacterium* constitute the pathogenic organisms of the gram-negative nonspore-forming rods. Other gram-negative nonspore-forming anaerobic rods are of much less clinical significance. *Bacteroides* and *Fusobacterium* differ from clostridia in that they always appear to be commensal with man, probably because of their fastidious requirements for growth and the inability to sporulate. They contribute to the normal flora of the mouth, the intestines, and the female genital tract. These organisms are strict anaerobes that can produce foul odor and gas. Many grow quite slowly, requiring a week or longer for identification and thus delaying application of the culture results to the care of the patient.

Most *Bacteroides* species are pleomorphic; however, *B. fragilis* is a nonpleomorphic nonfilamentous organism that makes distinction from *Escherichia coli* (with which it is often associated) difficult. *B. fragilis* is the most clinically significant of the gram-negative nonspore-forming rods and is the most frequently occurring anaerobic organism in clinical infections.[41] *B. fragilis* is the most common anaerobic organism causing septicemia.[12, 23, 40]

B. melaninogenicus is found in clinical infections, usually mixed with other species of *Bacteroides*. Although it is difficult to maintain this species in pure culture, it grows well if mixed with other anaerobes. The importance of this organism in establishing synergistic infections has been demonstrated by noting that mixed oral or intestinal anaerobic bacteria injected subcutaneously into animals do not cause infection without the presence of *B. melaninogenicus*.

The pathogenicity of the anaerobic gram-negative bacilli is poorly understood, although a variety of virulence factors have been ascribed to the *Bacteroides* group.[41] *Fusobacterium* and *Bacteroides* have been described as pathogens in infections located in multiple areas of the body. Prior to the antibiotic era anaerobic infections of the ear, nose, and throat regions were commonplace. More recently there has been a striking decrease in these types of infections, probably secondary to the widespread use of penicillin and tetracycline for the treatment of undiagnosed acute pharyngitis. Other infections associated with the gram-negative anaerobic organisms have included abscesses of the abdominal cavity and pelvis, acute appendicitis, lung, liver, and brain abscesses, infections of the gallbladder, perirectal infections, and pilonidal and sebaceous cyst infections.[8, 16, 32] *Bacteroides* infection often causes thrombophlebitis and secondary septic embolization to the liver, lungs, peritoneum, and joints. Bacteroidaceae bacteremia has been recognized with increasing frequency, with most *Bacteroides* bacteremias originating from the gastrointestinal tract, and most of the *Fusobacterium* bacteremias typically originating from upper respiratory sites.[8, 12, 23, 40]

Gram-positive cocci

Peptococcus and Peptostreptococcus. Peptostreptococcus differs from *Peptococcus* in that the former is the more significant pathogen and has been associated with anaerobic streptococcal myositis, septic abortion, liver abscesses, and empyema as well as with *Bacteroides* in a variety of mixed infections. Both are capable of producing a foul odor and gas. Present systems of classification for these organisms are generally deemed inadequate.[34] Both organisms occur nor-

mally in the vagina, mouth, and skin, but only *Peptostreptococcus* is found in feces. Because *Peptostreptococcus* has a similar commensal distribution as *Bacteroides,* it is not surprising that the anaerobic streptococci and *Bacteroides* are frequently found together in infections.

Attempts to demonstrate the pathogenicity of *Peptococcus* have been generally unsuccessful, and when these organisms are isolated they are most likely symbiotic to more pathogenic bacteria. Recently, however, *Peptococcus* has been shown to be a frequent cause of infected sebaceous cysts, breast abscesses, and finger infections.[28]

Gram-positive bacilli

Actinomyces. A. israelii and *A. naeslundii* have both been identified to be a part of the normal flora of the mouth. *A. israelii,* however, is the only pathogenic anaerobic fungus to occur in humans and results in infections of the cervical facial region (70%), abdomen (20%), and thorax (10%). *A. israelii* also occurs in the intestines of humans, but never exists as a saprophyte outside the body. It is extremely difficult to obtain a pure strain of *Actinomyces* in culture because of the close association of commensals; consequently, the properties of these complex cultures are difficult to interpret. Most strains of *A. israelii* are obligate anaerobes and will not grow on Sabouraud medium, which typically supports fungal growth. Clinical infections by this organism are always endogenous, complex, and accompanied by anaerobic cocci, *B. melaninogenicus, Actinobacillus actinomycetemcomitans,* and staphylococci. These concomitant organisms are effective because they lower the oxidation-reduction potential and secrete enzymes that facilitate tissue invasion by disrupting the mechanical structure of the tissues. "Sulfur granules" can usually be detected in the purulent material obtained from *Actinomyces* infections. The gram-positive rods result from fragmentation of the short branching hyphae and can often be confused with those of *Propionibacterium acnes,* but the catalase-positive activity of the latter will distinguish the two organisms.

Propionibacterium. The anaerobic diphtheroid *Corynebacterium acnes* has been reclassified as *Propionibacterium acnes.* This organism is significant because it is probably the most prominent bacteria of the normal skin flora and is often a contaminant in mixed cultures. It also occurs in the mouth and in the intestinal tract. *P. acnes* can be confused with *A. israelii.* Rarely do these bacteria occur in pure cultures or cause infection. In a recent study of anaerobic bacteremia,[40] 264 patients had positive blood cultures, of which 151 were positive for *P. acnes.* However, only one of the 151 patients had clinically significant bacteremia. In rare instances, *P. acnes* has been implicated as a primary pathogen in cases of sinusitis, infected prosthetic heart valve, and endocarditis either with or without rheumatic heart disease.

Other gram-negative nonspore-forming rods *(Eubacterium, Bifidobacterium,* and *Lactobacillus)* have been associated with clinical infections but the significance of these bacteria is not known.

Gram-negative cocci

Veillonella. Veillonella is the only gram-negative anaerobic cocci in man. It is strictly anaerobic and is found normally in the mouth, upper respiratory tract,

vagina, and intestinal tract. Strains of *Veillonella* have been identified from human material such as abscesses, cysts, pleural fluid, and bronchial infections. Usually they occur with other anaerobic or aerobic bacteria. Their role in infection is not known, but the consensus of opinion is that they are contaminants and not pathogens.

GENERAL CHARACTERISTICS OF ANAEROBIC INFECTIONS

Incidence

A survey of the literature reveals an unequivocal increase in the recovery of anaerobic organisms from clinical infections.* Several factors have contributed to the increased incidence of anaerobic infections. Improved culture methods may be a major reason for identifying more anaerobes. A higher absolute incidence of anaerobic infections without any change in culture techniques has occurred, although the effect of a greater awareness of these organisms is difficult to evaluate. The more effective control of aerobic infections by antibiotics may also have contributed to the recent prominence of anaerobic bacteria. In a 6-month period during 1968 at the Mayo Clinic, 26.4% of 1223 bacteriology specimens contained one or more anaerobes and 39.5% of all positive cultures had anaerobic organisms.[41]

Mixed flora

Specimens positive for anaerobic organisms contain anaerobes alone in 35% of cases and a combination of aerobes and anaerobes in 65% of cases.[41] In the 35% with only anaerobes present, 15% have a single anaerobe and 20% have two or more anaerobes. Thus in cultures positive for anaerobes, 85% have one or more additional organisms, either aerobic or anaerobic. Up to nine different kinds of anaerobes have been recovered from some infections. *Bacteroides* and *Peptostreptococcus* usually coexist and can be recovered from the same specimen in two thirds of cases.

The aerobic bacteria that are recovered most frequently from anaerobic infections include nonhemolytic streptococci, *Staphylococcus epidermidis*, coagulase-positive strains of *Staphylococcus aureus*, *Proteus*, and *E. coli*.[34]

Endogenous etiology

Most of the clinically significant anaerobes are commensals, with only some clostridial species able to exist away from the human body (Table 16-1). Not surprisingly, all of the anaerobic infections, with the exception of some clostridial infections, are endogenous in origin. Practically all of the clinically important anaerobes are present in the mouth and the intestine. The female genital tract contains *Clostridium*, *Bacteroidaceae*, *Peptostreptococcus*, and *Veillonella*, whereas the skin harbors just *Peptostreptococcus* and *Propionibacterium*, and the soil carries only *Clostridium*. Almost all cases of botulism, most cases of tetanus, and some cases of clostridial gas gangrene and clostridial anaerobic cellulitis are exogenous in origin. The incidence of tetanus in the United States seems to vary directly with the frequency with which *C. tetani* is found in the soil. Because of the commensal nature of the anaerobic organisms, there must be alterations in local

*See references 7, 8, 11, 19, 23, 40, and 41.

Table 16-1. Location of commensal anaerobes

	Mouth	Intestine	Vagina	Skin	Soil
Clostridium	OCC	+	OCC	0	+
Bacteroides	+	+	+	0	0
Fusobacterium	+	+	+	0	0
Peptostreptococcus	+	+	+	+	0
Actinomyces	+	OCC	0	0	0
Propionibacterium	+	OCC	0	+	0
Viellonella	+	+	+	0	0

+ = present; 0 = absent; OCC = occasional.

or systemic factors that permit invasion and subsequent infection to occur. A variety of predisposing conditions that will be enumerated later in this discussion can effect the necessary changes. Moore et al.[26] were able to demonstrate that of 40 different species of anaerobes isolated from human infections all but three or four were also present in the normal intestinal tract.

Gastrointestinal flora

Most clinicians do not appreciate the significance of the gastrointestinal flora or the role that these microorganisms play in infection and disease. The importance of gastrointestinal bacteria has been stressed in recent reviews,[10, 26] and several important facts pertaining to anaerobes have been emphasized. The highest concentration of anaerobic organisms in the human body occurs in the colon. The anaerobic bacteria in the colon outnumber the aerobic bacteria 1000:1. The bacterial content of the colon per gram of feces is approximately, with *Bacteroides,* 10^{11}/gram; with *Bifidobacterium,* 10^{10}/gram; with *Clostridium,* 10^{5}/gram; and with *Veillonella,* 10^{4}/gram. The coliforms are the most prevalent aerobic organisms in the colon and are present in concentrations of 10^{8} to 10^{9}/gram of feces. *E. coli* is most commonly recovered and is present in 95% of normal patients; *Klebsiella* and *Aerobacter* occur in 10% and 2% of people, respectively.

The mouth contains a mixed flora composed of *Bacteroides, Fusobacterium, Streptococcus, Veillonella,* and *Lactobacillus.* The stomach contains predominantly *Lactobacillus* in amounts of 10^{1} to 10^{4} viable bacteria/gram of contents, depending on whether the stomach is empty or full. In the small intestine the aerobic bacteria are most common, with *Lactobacillus* and *Enterobacter* increasing in amount from 10^{5} proximally to 10^{8} in the distal ileum.

The incidence of anaerobes in bile is not known except that 20% of bile cultures in the presence of disease will show clostridia.[17] Of interest is that the *Bacteroides* species in the mouth are generally sensitive to penicillin, whereas those from the colon are often resistant. This explains the fact that *Bacteroides* infections of the lungs, head, and neck regions will usually respond to penicillin therapy.

The clinical importance of the gastrointestinal flora lies in the disease entities that arise when there is an abnormal balance of organisms or when the organisms gain access to tissues beyond the bowel lumen. The stagnant loop syndrome and its variants, for example, are thought to result from the overgrowth of anaerobes in the small intestine and the resulting deconjugation of bile salts, which prob-

ably causes the steatorrhea in these patients.[10] Injury to the colon or lower small bowel provides an opportunity for the massive seeding of either a localized area or the entire peritoneal cavity with anaerobes, primarily *Bacteroides*. The use of only aminoglycoside antibiotics such as neomycin and kanamycin that are ineffective against most anaerobes to "sterilize" the colon prior to operation does not seem logical when the primary organism in the colon is *Bacteroides*, and therefore only 1% of the total colon bacteria is sensitive to the aminoglycoside antibiotics.[12]

Similarly, the choice of antibiotics that are not effective against *Bacteroides* for parenteral administration or peritoneal lavage in the treatment of colon disruption seems equally poor. Moreover, suppression of the normal flora may lead to overgrowth of enteric pathogens, and some investigators have commented that the preoperative use of antibiotics for preparation of the colon may predispose to gram-negative anaerobic rod bacteremia.[12, 23, 32] The endogenous nature of many anaerobic infections is supported by the close proximity of the infection to the gastrointestinal tract, i.e., perirectal and pilonidal abscesses, appendiceal abscesses, and colon anastomosis leaks with subsequent abscess formation.

Oxidation-reduction state

An important factor in anaerobiosis is the oxidation-reduction state of the tissues or media in which the anaerobic organism is grown. The oxidation-reduction potential (Eh) is a measure of the tendency of a system to give up electrons. A low Eh facilitates anaerobic growth, and a low pH permits anaerobic growth at a higher oxidation-reduction state. Normal tissue has an Eh of +120 mv. The colon tract has an Eh of about –250 mv, which is the result of the metabolic action of bacteria.[26] Prereduced anaerobic sterilized (PRAS) media have an Eh of –100 mv, which will permit the growth of most anaerobic organisms.

The most common cause of a clinically lowered Eh is the anoxia of tissues that may result from vascular injuries, compression, hypothermia, shock, tissue edema, or poor perfusion. The anoxia produces acidosis that further facilitates anaerobic growth. Tissue destruction also leads to a decreased Eh and may be the result of vasoconstrictive drugs, infection, or trauma. Other causes of a lowered Eh include foreign bodies, aerobic infections such as those caused by *Streptococcus pyogenes*, and ionized calcium salts.

Predisposing conditions

Many factors create conditions that predispose patients to anaerobic as well as other types of infection; some of the most common appear in the following list.

Collagen disease
Corticosteroid administration
Immunosuppression therapy
Cytotoxic agent administration
Diabetes mellitis
Malignancy
  Colon, uterus, lung
  Leukemia
Preoperative bowel sterilization
Acatalasemia
Gastrointestinal and female pelvic surgery

Gastrointestinal trauma
Human and animal bites
Decreased Eh
  Tissue anoxia and destruction
  Aerobic infection
  Presence of foreign body or calcium salts
Trauma and burns
Peripheral vascular disease

Patients with impaired defense mechanisms are susceptible to a variety of microorganisms, including viruses, protozoa, fungi, and bacteria. Finegold et al.[13] have thoroughly reviewed the literature as well as documenting their own experience with regard to anaerobic infections in the compromised host. All the conditions that predispose to infections in general predispose to anaerobic infections as well. There is no conclusive evidence that corticosteroid therapy, leukopenia, hypogammaglobulinemia, tumor therapy, collagen disease, splenectomy, or organ transplantation predispose to anaerobic infections any more than they do to infections in general. Although diabetes mellitus occurs with the same frequency among persons with anaerobic infections as it does in the general population, there does seem to be a predisposition toward concurrent anaerobic cholecystitis and osteomyelitis.

Malignancy, particularly solid tumors of the colon, uterus, and lung as well as leukemia, is a prominent underlying condition in 16% of all anaerobic infections reported in the literature. There are several factors accounting for the association between solid tumors in these locations and the presence of anaerobic infections. Obstruction, stasis, and tissue necrosis cause a lowering of Eh that results in favorable circumstances for anaerobic growth. Moreover, the mucosal surfaces of the colon, genital tract, and upper respiratory system are inhabited by a variety of anaerobic organisms in large numbers. A close correlation between clostridial sepsis and malignancy has been demonstrated.[1] A propensity to infections in general might best explain the anaerobic infection in these individuals.

Preoperative bowel preparation with a variety of antibiotics, particularly the aminoglycosides, appears to favor anaerobic infections following operations on the colon.[13, 32] There is insufficient data available, however, to reach a definite conclusion about the efficacy of preoperative "bowel sterilization" prior to colon surgery.

Acatalasemia, a condition in which there is a genetic lack of catalase in the blood, may predispose to anaerobic infections. This situation is confusing, as hydrogen peroxide leads to the destruction of anaerobes and catalase decomposes hydrogen peroxide. However, hydrogen peroxide oxidizes hemoglobin, and the resulting methemoglobin lacks normal oxygen-carrying capacity and thus causes local tissue necrosis—permitting anaerobes to flourish.

The increased incidence of anaerobic infections associated with operations on the gastrointestinal tract and female genitourinary system is primarily a result of the frequency of anaerobic commensals in the operative area. Penetrating wounds of the gastrointestinal tract, particularly those of the colon and distal small bowel, result in an increased incidence of anaerobic infections. The use of antibiotics that are effective against anaerobic organisms has been shown to de-

crease the number of anaerobes recovered from abdominal surgical wounds following colon-perforating trauma.[37]

Human as well as animal bites have been associated with synergistic infections that involve a variety of microorganisms, both aerobic and anaerobic, that are found in the mouth. Usually lacerations from this cause are not closed because of the high incidence of wound infection.

All the previously discussed factors that cause a decreased Eh are directly contributory to anaerobic infections. These include tissue anoxia, trauma, aerobic infections, the presence of foreign bodies and calcium salts in the wound, burns, and peripheral vascular disease.

Location and syndromes

Although infections caused by or associated with anaerobes are myriad, the location and/or clinical circumstances of certain infections often strongly suggests the presence of anaerobic organisms. The serious nature of anaerobic infections requires their prompt identification. A high index of suspicion will not only result in appropriate examination of the clinical material (gram staining and anaerobic cultures), but will also enable proper therapy to be instituted at the earliest possible moment. Many of the anaerobic infections are not distinctive enough on their own to be differentiated from aerobic infections (i.e., *Bacteroides* septicemia). Others, however, can be identified by their locations or specific syndromes. The following list offers a synopsis of infections commonly associated with anaerobic organisms.

Common locations of anaerobic infections
- Brain abscess
- Oral infection
- Chronic otitis media
- Pulmonary infection
  - Lung abscess
  - Empyema
- Intra-abdominal abscess
- Appendicitis
- Diverticulitis
- Peritonitis
- Perirectal or pilonidal abscesses

Brain abscesses, foul-smelling otitis media, especially in the presence of a cholesteatoma, and jaw infections, especially after tooth extraction or trauma, are in the majority of cases caused by anaerobes. Putrid lung abscesses, aspiration pneumonitis, and the often associated empyema are all strongly suggestive of anaerobic organisms. Intra-abdominal infections involving the liver, the subphrenic spaces, the interloop areas, the pelvis, and the tubo-ovarian region contain anaerobic organisms probably in a majority of the cases.[3] Peritonitis from a variety of causes but most commonly from perforation of the bowel as well as appendicitis and diverticulitis contains recoverable anaerobic organisms in a large percentage of cases. Perirectal and pilonidal abscesses typically have a rather foul odor, and although *E. coli* is the predominant organism cultured, it is the anaerobes *Bacteroides* and *Peptostreptococcus* that are responsible for the foul odor.

The following is a list of the syndromes frequently associated with anaerobic organisms.

Common syndromes of anaerobic infections
- Postabortal and puerperal infections
- Wound infections following bowel, gallbladder, gynecologic surgery
- Septic thrombophlebitis
- Gas-forming infections
- Putrid infections
- Septicemia with malignancy, diabetes, steroids, or negative blood cultures
- Tetanus
- Botulism

The circumstances that surround many infections make an anaerobic etiology highly likely. Infections of the uterus following abortion or delivery are most frequently caused by *Bacteroides* and anaerobic streptococci. The dreaded clostridial septicemia following criminal abortion is the most serious of uterine infections, producing circulatory collapse, jaundice, hemolysis, and renal shutdown with a 50% mortality in the face of renal failure. Wound infections that follow operative procedures on the colon, biliary tract, and female pelvic structures often reveal anaerobic organisms. Although many reviews of subphrenic abscesses fail to mention anaerobes as the etiologic organism, the frequent association of anaerobes and intra-abdominal abscesses is well established, and only a lack of proper culture technique has lead to an opposite conclusion.

Anaerobic infections must be suspected when septicemia occurs in association with malignancy, diabetes, corticosteroid administration, or the use of antibiotics that are ineffective against anaerobes and blood cultures remain repeatedly negative.[12, 14] Septic thrombophlebitis can be the result of an anaerobic infection in the area of vein inflammation. Typically, *Bacteroides* and anaerobic streptococci have a tendency to cause local thrombophlebitis and result in septic pulmonary emboli. Anaerobic infections of the oral pharynx can result in thrombophlebitis of the internal or external jugular veins, which is more easily recognized than the abdominal or pelvic thrombophlebitis that may accompany anaerobic gynecologic infections.

The clinical syndromes that involve gas production in the tissues or foul-smelling exudates are the most easily recognized clinical manifestations of anaerobic infections. Although the presence of gas in tissues, either manifested by crepitance or seen on x-ray examination, is recognized to be a classic manifestation of clostridial infection, it is not generally recognized that infections with other anaerobic organisms *(Bacteroides* and *Peptostreptococcus)* can also cause similar findings. The presence of gas in clostridial cellulitis and peptostreptococcal and *Bacteroides* infections is more easily identified than the presence of gas in typical "gas gangrene" caused by *C. perfringens.* This is because there is a greater degree of edema and swelling present with "gas gangrene." Yet it has been noted that significant gas production can occur with clostridial myonecrosis, even to the extent of filling the femoral vein. In the presence of diabetes, *E. coli* and *Klebsiella* have been reported to cause gaseous infections, but anaerobes have not been excluded in the published cases regarding these two organisms.[16] However, coliform organisms do ferment and can result in clinical gas production. There have been suggestions that even *Staphylococcus aureus* may cause clinical gas production.[2] *Pseudomonas* and *Proteus* are not associated with clinical gas formation.

The presence of a putrid exudate is typical of anaerobic infections, particularly

those caused by *Bacteroides* and *Peptostreptococcus*. The absence of foul-smelling pus, however, does not rule out the presence of an anaerobe. *E. coli* and *Streptococcus faecalis*, contrary to common belief, do not produce a putrid or feculant odor. The frequent association of anaerobic bacteria with *E. coli* and *Streptococcus faecalis* accounts for the foul smell commonly associated with these two aerobes.

Tetanus, botulism, and food poisoning due to clostridial organisms are the results of toxins and are more properly thought of as intoxications rather than infections per se.

LABORATORY DIAGNOSIS

The laboratory methods used to diagnose anaerobic infections may be examined in four parts. The first involves proper technique in obtaining representative specimens; the second concerns immediate examination of the material; the third deals with correct transportation of the material; and the last considers isolation and identification of the organism(s) by a variety of culture methods.

Specimen sampling

Because most of the anaerobes associated with infections are normally found on the body as commensals, it is important to avoid contact with the normal flora when a culture is taken; otherwise misleading results will be obtained. Specimens of blood and spinal fluid that are normally sterile only require skin sterilization prior to obtaining cultures. Abscess collections are best obtained by preparing the skin or mucous membranes with an antiseptic solution followed by needle aspiration rather than obtaining open samples with a swab. Urinary cultures can be contaminated with uretheral flora even from a midstream specimen, and thus suprapubic aspiration is preferred. Pulmonary specimens should be obtained via transtracheal aspiration. Samples of expectorated sputum as well as those obtained by bronchoscopy are always contaminated by the anaerobic organisms in the mouth. During debridement it is best to obtain several pieces of muscle or soft tissue from the deep parts of the dissection for culture and histologic examination.

Microscopic examination

Examination of the specimen by gram stain, dark field, and histologic methods not only helps assess the clinical situation initially, but also can provide useful information in interpreting the significance of culture results. An abundance of gram-positive rods indicates the presence of clostridial organisms, the significance of which depends on the clinical setting. Plump gram-positive rods with few leukocytes are indicative of clostridial myonecrosis (gas gangrene), whereas an abundance of leukocytes is compatible with the less severe clostridial cellulitis. Chains of streptococci and many leukocytes are seen in anaerobic streptococcal myonecrosis. With severe clostridial septicemia, organisms have been identified on gram-stained smears of peripheral blood. Pleomorphic gram-negative rods are likely to be *Bacteroides;* however, *B. fragilis* may be uniform rather than pleomorphic and thus indistinguishable from the frequently present *E. coli*. Delicate gram-positive branching rods are characteristic of *A. israelii*, but may have to be distinguished from *Nocardia asteroides* by acid-fast stains. Sulfur granules are aggregates of the *Actinomyces* organisms.

Transportation of specimen

Poor transportation techniques and delays in culturing specimens are the most frequent mistakes in attempting to isolate anaerobic organisms. Some anaerobes will not survive 30 min in an aerobic environment. Delays in culture may permit an overgrowth of facultative organisms that grow faster than the anaerobes. A variety of acceptable transportation techniques are available and include (1) a capped specimen syringe with air expelled; (2) a carbon dioxide–filled tube; and (3) prereduced anaerobically sterilized (PRAS) liquid medium. Negative aerobic and anaerobic cultures when organisms are present on gram stains of the clinical material are often caused by errors in transporting the specimen to the laboratory.

Culture

Intelligent interpretation of anaerobic culture reports requires appreciation of the principal methods and difficulties in anaerobic culture work.[20] The microbiologist must be well versed in the area of aerobic bacteriology because of the frequent association of facultative organisms with obligate anaerobes. Aerobic bacteriology is therefore an integral part of the investigation of anaerobes. To distinguish between the facultative organisms and strict anaerobes, aerobic as well as anaerobic cultures are performed. When there is evidence of bacterial growth on the anaerobic culture in the absence of growth on the aerobic culture, the presence of anaerobes can be assumed.

Another method of identifying anaerobic organisms involves the use of selected media that contain antibiotics that prevent the growth of aerobes. Growth on these media is evidence of anaerobic organisms. A presumptive diagnosis of anaerobic infection can be made when the gram stain indicates the presence of organisms, but there is no growth on properly prepared aerobic cultures. The difficulties in anaerobic microbiology are increased by the slow growth of these organisms (some requiring 7 days or longer for the organisms to be identified). In addition, because of the frequent occurrence of mixed infections, multiple subculturing techniques must be instituted in order to isolate each specific organism. Finally, when the specific anaerobe has been identified, its anaerobic nature must be confirmed by the absence of growth in air, a process that requires several additional days.

A variety of media are available for the culturing of anaerobic organisms. The worst of these is probably thioglycollate broth, which is the medium commonly used to routinely grow anaerobes in most laboratories. The best media presently in use are the PRAS media that are dispensed, autoclaved, and innoculated in the absence of oxygen. However, because most of the extremely fastidious anaerobic bacteria do not cause human infections, the use of anaerobic jars is entirely satisfactory for the workup of most clinical material.

Morphologic features and gram staining can usually be performed within 2 to 3 days in order to identify the genus to which an anaerobe belongs. Identification of the particular species is more involved and requires a series of carbohydrate fermentation tests, and in the case of clostridial organisms, various toxins elaborated by the organism must be identified. These procedures take considerable time. Recent advances in the use of liquid and gas chromatography have now made it possible to identify species of anaerobes within 24 hr.

TREATMENT

Early and prompt diagnosis and treatment are always important. Delay in the treatment of clostridial myonecrosis or a brain abscess could be catastrophic. Treatment must not wait for culture reports in any case where there is a presumptive diagnosis of a potentially serious anaerobic infection. Rather, therapy must often be guided by a high index of suspicion for a particular anaerobic organism or clinical syndrome. Treatment is based on a few simple and relatively consistent guidelines that involve the removal of dead tissue, the preservation of normal tissue, and the neutralization of toxins.

Debridement and drainage

The sine qua non of treatment in almost all anaerobic infections is the debridement of dead and necrotic material that provides an excellent medium for the growth of anaerobes. This applies to radical debridement or amputation necessary in clostridial myonecrosis as well as excision and drainage of small puncture wounds causing tetanus. Thorough debridement must remove all dead tissue, and the line of resection should be taken back to bleeding tissue and contractile viable muscle. Incision alone will suffice in some circumstances, as with perirectal abscesses and infected pilonidal cysts. Similarly, intra-abdominal abscesses that frequently contain anaerobes are often adequately treated by wide incision and drainage without excessive debridement. With deeper abscesses, antibiotic therapy as well as drainage will be necessary to control the systemic manifestations of the disease and prevent recurrence.

The only types of anaerobic abscesses that do not require incision and drainage are the putrid lung abscesses. In the majority of cases they will improve with antibiotic therapy (usually penicillin G), postural drainage, and occasionally bronchoscopy.

Antibiotics

Antibiotics must be considered adjuvant therapy in the treatment of anaerobic infections since the mainstay of therapy is debridement. Nevertheless, antibiotics do play an important role. Because of the frequent occurrence of mixed synergistic infections, it is important to treat not only organisms recovered from the blood but also those present in the material from the source of seeding.[12]

At present there is no standard in vitro method of determining the antibiotic sensitivity of anaerobic bacteria, and it is difficult to interpret sensitivity results between different laboratories. However, progress is being made in attempts at standardizing disk susceptibility with agar dilution techniques.[36] Except for blood culture isolates, routine antibiotic susceptibility testing of anaerobes cannot be performed with the same facility and frequency as is done with aerobes. Periodic testing by each laboratory must suffice for the present. Because of the differences between laboratories in determining in vitro sensitivities, especially with regard to tetracycline vs *Bacteroides*, there is a clear need for well-controlled prospective clinical studies of the antibiotic efficacy in anaerobic bacteremia.[24]

Despite the aforementioned difficulties, there is good information on antibiotics and their effect on anaerobic organisms (Table 16-2).[6, 11, 24, 40] Nearly all anaerobes are resistant to the aminoglycosides (streptomycin, kanamycin, neomycin, and gentamicin) and polymyxins. In general all anaerobes are sensitive to

Table 16-2. Antibiotic sensitivities of anaerobes

	Clostridium	Anaerobic cocci	*Bacteroides fragilis*	Other *Bacteroides* species	*Actinomyces*
Penicillin	E	E	P	E	E
Lincomycin	G	E	P	E	E
Cephalothin	G	G	P	G	—
Clindamycin	E	E	E	E	E
Chloramphenicol	E	E	E	E	E
Metronidazole	E	G	E	E	E
Rifampin	E	E	E	E	E
Tetracycline	G	G	P	G	G
Erythromycin	G	E	P	P	G

E = excellent; G = good; P = poor.

penicillin G except *B. fragilis*. Therefore the frequently used antibiotic combination of penicillin G and streptomycin will not be effective against *B. fragilis* infections. Lincomycin has a similar spectrum of activity to penicillin G and may be useful when there is a history of penicillin allergy. Cephalothin inhibits a majority of anaerobes, excluding certain species of *Bacteroides*, but it is generally less effective than penicillin or lincomycin. Chloramphenicol is effective against *all* anaerobes, including *B. fragilis*. Similarly, clindamycin has also been shown to be effective against *all* anaerobes, both in vitro and in some clinical studies. Although metronidazole, the antiprotozoal agent used effectively in Vincent's angina, is also highly effective against all strains of anaerobes, including *B. fragilis*, it has not been released for use against anaerobes. Rifampin inhibits all anaerobic strains and is bactericidal for *B. fragilis*, but it is an experimental drug and not available at present for use in anaerobic infections. Tetracycline, although once an effective anaerobic antimicrobial, especially against *B. fragilis*, has been shown recently to be ineffective against a large number of anaerobes, especially *B. fragilis*,[24, 40] and is no longer the drug of choice in anaerobic infections.

Bacteroides species are generally resistant to ampicillin, cephalothin, carbenicillin, tetracycline, lincomycin, erythromycin, and vancomycin and are sensitive to chloramphenicol, clindamycin, rifampin, and metronidazole. Words of caution have been raised against the indiscriminate use of clindamycin less it become ineffective against *B. fragilis* as did tetracycline. In addition, the recent association of colitis with this drug should be considered. *Bacteroides* species isolated from the upper half of the body are generally sensitive to pencillin G, and those from the lower half are resistant. This is primarily because *B. fragilis* is the species resistant to penicillin G and more frequently resides in the lower gastrointestinal tract. Other *Bacteroides* species, sensitive to penicillin, reside in the mouth and upper airways. *A. israelii* is sensitive to most antibiotics, with penicillin and tetracycline the agents of first choice. Clostridial species are also sensitive to a majority of antibiotics, with penicillin, tetracycline, and chloramphenicol being most effective.

Oxygen therapy

It is only natural that attempts at increasing the oxygen tension of tissues should be tried in the treatment of anaerobic infections. To this end several procedures have appeared effective.

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy[21] was popularized by Brummelkamp. In 1966 he published his results on 55 patients with gas gangrene treated with hyperbaric oxygen and noted an overall mortality of 18%. With hyperbaric oxygen therapy, patients are subjected to three atmospheres of pressure while inhaling 100% oxygen, thus increasing the amount of dissolved oxygen in the plasma 15-fold. Arterial oxygen tensions in the range of 1200 to 1700 mm Hg are optimal. Exposures last usually from 60 to 90 min and are repeated every 8 to 12 hr as necessary. In most circumstances only four to five exposures are required. Oxygen at high pressure is toxic for bacteria, but it also seems to behave as a general protoplasmic poison. Consequently, care should be taken to minimize the degree of oxygen exposure. Oxygen intoxication manifested by sweating and local convulsions can be avoided by sedation before treatment. Myringotomy may be necessary in the unconscious patient to prevent rupture of the tympanic membrane. An increasing number of investigators believe that this is a significant and important aspect of the treatment of clostridial myonecrosis. All, however, caution against the mistake of utilizing the hyperbaric oxygen treatment in lieu of proper surgical debridement. Other investigators do not feel that well-controlled studies have yet produced conclusive results and contend that this mode of therapy should be considered experimental for the present.[2]

Reports both for and against the use of hyperbaric oxygen in the treatment of tetanus have appeared.[15] It cannot be recommended at the present time, however, as it is not the proliferation of bacteria but rather the perfusion of the body with toxins that is the etiologic basis of tetanus.

Hydrogen peroxide. Often 3% hydrogen peroxide is used to irrigate anaerobically infected wounds because the oxygen released by the action of tissue catalases destroys anaerobes. This method is valuable in wounds covering large areas, particularly those involving the thighs and buttocks where continued fecal contamination is difficult to control. Continuous bathing of the wound with hydrogen peroxide may be performed by using an assortment of tubes and sump irrigating devices. A potential complication of this therapy could involve the appearance of false crepitance resulting from the release of oxygen bubbles into the tissues.

Zinc peroxide paste. Although commonly referred to in the older literature, the use of zinc peroxide paste is only occasionally mentioned in recent articles dealing with anaerobic infections.[14] It may be useful in the treatment of Meleney's ulcer, and its local application may effect dramatic improvement in some difficult anaerobic infections.

Antiserum

The use of antitoxin in the treatment of gas gangrene is debatable. Some researchers believe that there is considerable value in the use of clostridial polyvalent antitoxin and recommend doses of 45,000 to 50,000 units for the treatment of gas gangrene, whereas other investigators advise against its use completely or state that its use is optional. However, the administration of antitoxin in the treatment of postabortal clostridial sepsis is a definite and important aspect in

the care of these patients. The hemolysis, shock, and renal failure associated with postabortal clostridial sepsis can be directly traced to a circulating alpha toxin (lecathinase) of *C. perfringens*, whereas in gas gangrene (clostridial myonecrosis) there is no hemolysis or clostridial toxin in the blood. Consequently, it has been proposed that the hypotension and toxic findings with clostridial myonecrosis are the result of products elaborated by the reaction of clostridial alpha toxin on muscle.

The use of tetanus-immune globulin (human), TIG(H), for the treatment of tetanus or as a prophylactic measure has been a definite advancement. Because TIG(H) is available in this country in adequate amounts, it is no longer necessary to use the heterologous tetanus antitoxin that is associated with a short in vivo half-life, allergic reactions, and delayed serum sickness.

A multivalent antitoxin to the common botulism toxins A, B, and F is available for the treatment of botulism.

Prophylactic measures

Thorough debridement of wounds and avoidance of primary closure when there is a significant chance of an anaerobic environment are important aspects in the treatment of traumatic injuries. Prevention of constrictions about the extremities either by bivalving casts or rewrapping tight circumferential bandages is important in the prevention of ischemic gangrene of the extremities. Antibiotics have been shown to be effective in the prevention of gas gangrene when given prior to trauma in experimental animals and probably do play a role in the treatment of clostridial myonecrosis and cellulitis by eliminating further spread of the infection. Sterilizing bowel preparations, as discussed previously, may lead to the overgrowth of anaerobes (primarily *Bacteroides*); this can subsequently result in an increased incidence of operative infections. The avoidance of preoperative antibiotic bowel preparation may be sound. Aspiration at the time of anesthesia, particularly during tonsillectomy, can be prevented in most circumstances. The early and effective treatment of head and neck infections with timely operative intervention and drugs will lessen the incidence of these infections leading to subsequent brain abscesses. Of all these measures, however, only immunization with tetanus toxoid has the potential for 100% effectiveness.

Heparin and vein ligation

In the presence of septic thrombophlebitis, typically caused by *Bacteroides* and/or anaerobic streptococci, there is usually evidence of vein involvement when the process is the neck. When septic pelvic thrombophlebitis exists, there is initially no evidence of vein involvement until central embolization occurs or there is massive obstruction of the iliac vessels, leading to leg enema. Heparin is given to prevent further thrombosis, although central embolization has occurred in the presence of heparin administration. Heparinase produced by *Bacteroides* may very well inactivate the heparin, thus negating any possible antiembolic effect.[12] In the presence of septic embolization to the lungs, ligation of the inferior vena cava and ovarian veins is indicated.

CLINICAL INFECTION

The almost unlimited variety of infections that are or may be caused by anaerobic organisms precludes an exhaustive discussion of each condition. It is

important, however, to be familiar with the most frequent infections caused entirely or in part by anaerobes.

Actinomycosis

A. israelii, the only known pathogenic anaerobic fungus in man, only rarely causes infections. Actinomycosis is more frequent in men and in individuals over 20 years of age. This disease is thought to be endogenous in origin because *A. israelii* is commonly found in the mouth, and there is no evidence of person-to-person transmission. Cultures of this infection typically reveal several organisms, including anaerobic cocci, *B. melaninogenicus, A. actinomycetemcomitans,* and staphylococci, that facilitate growth of *A. israelii* by lowering the Eh or by secreting enzymes that facilitate tissue invasion. Infections of the neck, jaw, and face account for 60% of the cases in man. Infections that usually follow trauma such as tooth extraction develop into hard swellings with draining sinus tracts. "Sulfur granules" can be seen in the purulent sinus tract discharges. Abdominal actinomycosis (20% of cases) may follow abdominal operation and results in a typically nonlocalized extensive infection with draining abscesses and sinus tract communications with the intestinal lumen. Abdominal actinomycosis often presents as a mass in the ileocecal region with sinus tracts to the skin following a history of acute appendicitis. The findings can mimic regional enteritis, tuberculosis, and malignant tumors. Surgical drainage is often not necessary, and antibiotic administration will usually result in cures without operative intervention. Thoracic actinomycosis (10% of cases) follows aspiration of purulent material from actinomycotic abscesses that communicate with the oral cavity. The pulmonary parenchyma, the pleura, and the thoracic wall may all be involved. Actinomycotic infections of the tear ducts, eyes, and female pelvic structures have been reported.[34]

The primary treatment of actinomycosis involves antibiotics rather than surgery. Penicillin G, 10 million units daily, or tetracycline, 2 Gm daily, are the drugs of choice and are given for several weeks after cure appears to have been effected. Disseminated actinomycosis usually results from pulmonary lesions and can be manifested by a persistent long-term septicemia, brain abscesses, or multiple painful erythematous skin lesions. Long-term antibiotic treatment of 6 months or more may be necessary to clear the septicemia.

Botulism and tetanus

Botulism and tetanus are diseases that are more properly thought of as intoxications rather than infections, and the anaerobic connotations so essential in analyzing other infectious processes are not nearly so important in these entities except for the prophylactic and therapeutic treatment of the local infection in tetanus.

C. botulinum elaborates six different types of neurotoxins (A to F) that are absorbed from the stomach and are fixed in peripheral nerves where they block transmission of the cholinergic nerve fibers. Toxins A and E cause most human cases of disease and are associated with a 70% mortality, whereas type B appears less commonly and has a 20% mortality. A trivalent antitoxin against toxins A, B, and E is available for treatment. Botulism usually results from ingesting improperly prepared, home-canned foods. The signs and symptoms of nausea, vomiting, abdominal pain, diarrhea, and the central nervous system findings that

involve all the cranial nerves except the first and second usually occur 24 hr after ingestion. The diagnosis is usually made on the basis of clinical features and a history of canned food ingestion. Absolute confirmation of the diagnosis depends on the demonstration of botulinum toxin in the food or in the patient's serum. Therapy involves gastric lavage, ingestion of alcohol to precipitate the toxin, enemas of soap and olive oil to neutralize the toxin and prevent absorption, respectively, administration of trivalent antitoxin, and respiratory support.

Tetanus is not common in the United States, as only 150 cases on the average are reported annually. Much of the clinical information on tetanus comes from foreign countries where the disease is more prevalent. A recent monograph on tetanus by Furste and Wheeler[15] is recommended for a comprehensive review of the subject.

C. tetani is ubiquitous and no doubt contaminates many wounds. The tetanus organisms gain entry usually from a wound or rarely as a result of criminal abortion. Tetanus can be a complication of narcotic addiction when the drugs are injected. Neonatal tetanus is the result of rubbing the umbilical cord with dirt or animal dung. In one third of the cases no portal of entry can be identified. When local conditions are favorable, the organism grows without invasion and produces a powerful neurotoxin that spreads to the gray matter of the spinal cord along peripheral motor nerve trunks. There it diminishes central inhibition of spinal cord activity, resulting in increased motor activity and spasticity. Early signs and symptoms appear within 2 weeks from the time of injury and include irritable muscles about the wound, trismus, dysphasia, nuchal rigidity, headaches, backaches, general irritability, tachycardia, anxiety, and sweating. Muscles of the chest, abdomen, back, and extremities become progressively affected, leading to generalized tonic convulsions that can be precipitated by a variety of external stimuli.

The diagnosis of tetanus depends on the clinical signs and symptoms, as in only 13% of cases can *C. tetani* be recovered from the wound, and the finding of tetanus organisms in a wound is no assurance that toxin is being produced.

The treatment of established cases of tetanus involves several modalities of care. Five thousand units of TIG(H) is administered intramuscularly proximal to the area of injury. TIG(H) is never given intravenously. Meticulous nursing care in a quiet, dark room with adequate sedation of the patient is essential. Sedative and muscle relaxant drugs commonly used include barbiturates, paraldehyde, diazepam, meprobamate, *d*-tubocurarine, and succinylcholine. The wound is thoroughly debrided and penicillin given, although the benefit of systemic antibiotics is probably minimal. Most patients require tracheostomy and continuous artificial respiration with frequent attention to tracheal toilet. Somewhat controversial is the intrathecal injection of tetanus antitoxin and prednisolone for the acute treatment of tetanus. Despite proper and early care, the mortality associated with tetanus in the United States is 50%.

The best method of managing tetanus is prevention by immunization with tetanus toxoid prior to injury. The absence of any case of tetanus in United States Army active duty personnel between 1954 and 1971 attests to the effectiveness of prophylactic immunization programs. Adsorbed tetanus toxoid is preferred over the fluid tetanus toxoid both for initial immunization and booster doses. Basic immunization with adsorbed toxoid requires three injections, the second 1 month

after the first and the third 6 months to 1 year after the second. Booster doses are recommended every 6 to 10 years. More frequent boosters are unnecessary and increase the incidence of hypersensitivity reactions.

Each wounded patient must be individualized with regard to tetanus prophylaxis. The adequacy of prior immunization, the status of hypersensitivity to tetanus toxoid, and the severity, contamination, and circumstances of the injury are important factors bearing on the type of prophylaxis that is best employed. The following outline gives a routine for tetanus prophylxis in wounded patients based on the recommendations of the Committee on Trauma of the American College of Surgeons.[4]

I. Patient previously immunized
  A. Immunized within the past 10 years
    1. To most patients give 0.5 ml of adsorbed tetanus toxoid, *unless it is certain* that a booster has been given within the previous 5 years.
    2. To those with severe, neglected, or old (more than 24 hr) tetanus-prone wounds, give 0.5 ml of absorbed toxoid, *unless it is certain* that a booster was administered within the previous year.
  B. Immunized more than 10 years previously
    1. With clean or minor wounds, give 0.5 ml of adsorbed tetanus toxoid.
    2. With severe, neglected, or old (more than 24 hr) tetanus-prone wounds give
      a. 0.5 ml of adsorbed toxoid
      b. 250 to 500 units of TIG(H)
      c. Antibiotic therapy (optional)
II. Patient not previously immunized
  A. In clean minor wounds in which tetanus is most unlikely, give 0.5 ml of adsorbed tetanus toxoid as the initial immunizing dose.
  B. In all other wounds give
    1. 0.5 ml of adsorbed tetanus toxoid as the initial immunizing dose
    2. 250 to 500 units of TIG(H)
    3. Antibiotic therapy (optional)

When tetanus toxoid and TIG(H) are given simultaneously, separate syringes and needles and opposite arms should be used for administration. Oxytetracycline and penicillin are the antibiotics of choice when it is elected to give antibiotic therapy. Antibiotic therapy, however, cannot be relied on to prevent *C. tetani* growth in a wound. A satisfactory anamnestic response to adsorbed tetanus toxoid is not to be expected in the presence of agammaglobulinemia, acute radiation exposure, immunosuppressive drugs, or carcinoma of the breast. Under these circumstances antitoxin as well as the toxoid should be administered.

Thorough and immediate debridement of the wound is essential for the prevention of tetanus regardless of the immunization status of the patient. All nonviable tissue and foreign bodies should be removed and the wound irrigated with large quantities of normal saline solution.

Oral cavity infections

Many of the anaerobic infections of the oral cavity blend together over a spectrum of clinical findings. The frequent use of antibiotics, particularly penicillin, has resulted in a marked decrease in the anaerobic etiology of otitis media, tonsillitis, sinusitis, mastoiditis, dental abscesses, and osteomyelitis of the jaw. Cholesteatomas favor the growth of anaerobes, and a putrid discharge with otitis media, especially when associated with headaches, is a dangerous finding because

Fig. 16-1. Ludwig's angina with submaxillary and sublingual swelling causing mild respiratory distress.

of the possible sequence of mastoiditis, lateral venous sinus thrombosis, and finally brain abscess.

Fusospirochetal infections. Fusospirochetal infections of the oral region vary from a benign inflammation of the gingiva to acute necrosis of the gingiva, then necrosis of the mucosa of adjacent areas, and finally extensive destruction of the mucous membrane and underlying structures with the most devastating and far-ranging destruction labeled "cancrum oris" (noma). Fusospirochetal pharyngitis (Vincent's angina) also occurs. Furospirochetal infections are so designated because of the abundance of *Fusobacterium* and spirochetes that occur in these lesions. The proper diagnosis depends on the appearance and putrid odor. Demonstration of the organisms in histologic sections of the necrotic lesions is required for pathologic confirmation. Smears of the lesions are not useful because anaerobic organisms are normally present in the oral cavity.

Ludwig's angina. Ludwig's angina is an anaerobic infection that involves the submaxillary and sublingual spaces. Little pus is produced, but there is massive submaxillary and sublingual swelling that can cause dysphagia and dyspnea (Fig. 16-1). Incision and decompression of the area and occasionally tracheostomy are required in addition to treatment with penicillin.

Putrid infections. Putrid infections of the oral cavity are composed of a variety of foul-smelling purulent oral infections, usually caused by *Bacteroides* and *Peptostreptococcus* in association with dental procedures. Penicillin therapy and drainage usually suffice in controlling the infections. Hydrogen peroxide (3%) mouthwashes and good dental hygiene are important adjunctive measures. A serious complication of these infections is thrombophlebitis of the jugular venous

system, which may be the cause of as many as one third of all cases of *Bacteroides* septicemia.

Brain abscess

Anaerobes cause the majority of all nontraumatic brain abscesses.[18] *Peptostreptococcus* is most commonly cultured from brain abscesses, with *Bacteroides* next in frequency, followed by *Fusobacterium.* Often there is a mixture of organisms. A variety of organisms, including *P. acnes, Veillonella,* paracolon organisms, *Proteus,* and *Actinomyces,* have also been recovered. Areas of cerebral avascularity and the association of cyanotic congenital heart disease are predisposing factors. These abscesses can result from infections of the middle ear and mastoid region by direct spread, and from the oral, pharyngeal and pulmonary locations via septic embolization. A brain abscess usually presents with the clinical findings of a space-occupying cerebral mass. Headaches in individuals with cyanotic congenital heart disease or chronic otitis media may be an important clue. Spinal fluid findings may be inconclusive unless there is an associated meningitis. Gas-filled abscesses may occasionally be seen on x-ray films of the skull; however, cerebral angiography and radioisotope scans of the brain are usually required for a proper diagnosis. Needle aspiration of the abscess along with antibiotic therapy may occasionally produce successful results; however, in most instances drainage or preferably excision of the abscess is the therapeutic method of choice. Chloramphenicol and clindamycin are the primary drugs used because they provide adequate treatment against all anaerobic organisms. A prolonged course of treatment for 6 weeks or longer may be necessary to completely irradicate any persistent infection. The best chance of treating anaerobic infections of the brain is during the stage of cerebritis prior to abscess formation. Actinomycotic brain abscess usually results from septic embolization from the lungs.

Urinary tract infections

Anaerobic organisms cause 1% to 2% of all urinary tract infections. A variety of organisms have been identified, including *Bacteroides, Peptostreptococcus, Clostridium,* and *Actinomyces.* Bacteremia, instrumentation, and lymphatic spread, all usually in association with stones, are methods by which anaerobic organisms are introduced into the urinary system. Predisposing factors include malignancy, obstruction, and renal tuberculosis. Anaerobes constitute part of the normal flora of the urethral mucosa, and therefore to obtain representative anaerobic specimens it is usually necessary to perform suprapubic aspirations of the bladder. Anaerobic urinary tract infections often are manifested by gas in the tissues, gangrenous changes, and foul odor. Clostridial infections typically follow operations and are usually limited to the surgical wound.[16]

Pleuropulmonary infections

Pleuropulmonary infections are typically mixed, with anaerobes, aerobes, and facultative anaerobes present. *Bacteroides, Fusobacterium, Peptostreptococcus,* microaerophilic streptococci, and *C. perfringens* as well as the previously discussed *A. israelii* have all been recovered from pulmonary infections. Pneumonitis, lung abscesses, and empyema are the typical clinical presentations. Pleuropul-

monary anaerobic infections are usually suspected on the basis of putrid discharge; abscess formation; chronicity; predisposing conditions such as aspiration, pulmonary obstruction, dental procedures, or distal septic foci; and organisms on gram-staining of clinical material with failure to identify a pathogen on aerobic cultures. Obtaining the proper specimen for anaerobic culture is important. Sputum is unsatisfactory, as it is contaminated with anaerobic organisms from the mouth and oropharynx. Percutaneous transtracheal aspiration is required to obtain reliable specimens. Aspiration of pleural fluid or a lung abscess would also prove satisfactory. Pulmonary anaerobic infections do not commonly result in septicemia, and consequently blood cultures are usually negative. With pneumonitis, the clinical findings are often suggestive of malignancy, and most diagnoses are made on pathologic specimens obtained at exploratory thoracotomy.

Lung abscesses usually are the result of aspiration of a variety of materials into the tracheal bronchial tree. Predisposing conditions include depression of cough and cilia action by anesthetic drugs, alcoholic intoxication, or coma. The location of the pulmonary abscesses depends on the position of the patient when the material is aspirated. Since most individuals are in the supine position, pulmonary abscesses from aspiration are in the posterior segment of the right upper lobe and the superior segments of both lower lobes. Septic pulmonary embolization is typically multiple, bilateral, and located in the lower lobes. A variety of initiating factors that cause anaerobic septicemia may lead to septic pulmonary embolization.

Frequently anaerobic lung abscesses produce putrid material and show air fluid levels on x-ray examination. Abscesses in the pulmonary parenchyma may be treated primarily with antibiotics and without operative drainage or resection. Most abscesses will respond to penicillin in doses of 1.2 to 2.4 million units/day. The successful treatment of these abscesses without operative intervention is probably secondary to the vascularity of the lungs and the ability of the cavity to collapse after bronchial drainage.

Approximately 9% to 17% of all empyemas result from anaerobic infections. Typically they are a complication of pulmonary abscess and the organisms recovered are those previously mentioned. Unlike the treatment of a pulmonary abscess, empyema requires surgical drainage.

Female genital tract infections

The female genital tract contains a large variety of potential pathogens (Table 16-1) as well as the more benign coagulative-negative staphylococci and lactobacilli.[30] *C. perfringens* may be cultured from the genital tract in about 5% of normal women. As a result, there are a large variety of female genital tract infections that are caused by anaerobes. The most dramatic of these is infection of the uterus by clostridial organisms in association with pregnancy. The degree of infection may range from a localized invasion of the dead fetus and placenta to a florid involvement of the entire uterus with necrosis, perforation, peritonitis, and sepsis. Septic patients may manifest jaundice, hemoglobinuria, intravascular hemolysis, hypotension, and renal failure. The mortality with these findings is over 50%. Treatment entails surgical removal of the necrotic material (often necessitating hysterectomy), large doses of antibiotics, particularly penicillin, and the administration of polyvalent gas gangrene antitoxin.

Postabortal sepsis may also be associated with *Bacteroides* and anaerobic streptococci. Frequently *E. coli* occurs along with the anaerobes in postabortal sepsis. Usually intensive antibiotic administration, including chloramphenicol and kanamycin, is given for 24 to 48 hr prior to curettage of the uterus to permit the fever and toxicity to subside. At times immediate curettage is necessary.

Puerperal sepsis is most frequently caused by the anaerobic streptococci, but *Bacteroides* can also cause this entity. The anaerobic organisms are frequently associated with pelvic thrombophlebitis, unlike the aerobic bacteria that seldom produce thrombophlebitis.[33] Antibiotics, usually penicillin, constitute the major form of treatment. In the presence of recurrent septic embolization, ligation of the inferior vena cava and ovarian veins is indicated.

The most common anaerobic infections of the female genital tract are pelvic abscesses, chronic pelvic inflammatory disease, infections of the uterus, and Bartholin abscesses. *Bacteroides* and anaerobic streptococci are most commonly found, and the infections often have the typical putrid odor of anaerobes. There has been a general increased appreciation of the importance of anaerobic organisms in severe obstetric and gynecologic infections.[22 27]

Gas-forming infections

The presence of gas in tissues may be either traumatic or infectious in origin. Chest injuries, air hose injuries, hydrogen peroxide irrigations, and benzene injections are a few of the many traumatic causes of palpable crepitance.[2] Gas in the soft tissues may also be identified by auscultation and on x-ray films (Fig. 16-2). Infections that result in soft tissue gas formation may be caused by not only the clostridial organisms, resulting in the familiar "gas gangrene," but also by other anaerobic organisms (*Bacteroides* and *Peptostreptococcus*) as well as some facultative anaerobes (*E. coli, Enterobacter,* and *Klebsiella,* particularly in diabetics). Gas-forming infections may be grouped into four general categories: anaerobic cellulitis, infected vascular gangrene, clostridial myonecrosis, and streptococcal myositis.

It should be appreciated that the presence of *Clostridium* in wounds has three levels of significance. First, it may simply represent wound contamination, which occurs frequently and has no clinical significance. Second, it may take the form of anaerobic cellulitis in which there is a local infection without invasion of healthy muscle and no signs of systemic toxicity. There is, however, much gas in soft tissues. Third, clostridial organisms may cause true gas gangrene with destruction of viable muscle, much toxicity, and the appearance of relatively little gas in the tissues. It is the clinical findings that either make or refute the diagnosis of clostridial myonecrosis (gas gangrene).

Infected vascular gangrene results when arteriosclerotic peripheral vascular disease provides the conditions of ischemia for the proliferation of organisms under anaerobic conditions. A variety of anaerobes and/or facultative organisms can contribute to this entity, which is manifested by gradual swelling, black skin discoloration, abundant gas formation, and a foul odor. Dead muscle is present, but on the basis of poor blood supply and not bacterial invasion.

Peptostreptococcal myositis may be easily confused with clostridial wound infection and if not properly diagnosed may lead to an unnecessary amputation of the extremity.[5] This entity is manifested by a subacute onset of 3 to 4 days'

Fig. 16-2. Peptostreptococcal infection of left thigh with extensive gas infiltration of soft tissues extending proximal to inguinal ligament into retroperitoneal space.

duration, marked swelling of the extremity, a profuse exudate, a variable amount of gas production, and a foul odor. The muscle may appear to be involved but will usually contract when stimulated. Gram stain of the material shows many inflammatory cells and numerous gram-positive cocci without gram-positive rods.

The important differential features of these four clinical entities are outlined in Table 16-3. The two basic clostridial infections may be described as much toxicity and little gas with "gas gangrene" and much gas and little toxicity with anaerobic cellulitis. (The treatment of clostridial myonecrosis has been covered previously.) Infected vascular gangrene will often require amputation. Anaerobic cellulitis and streptococcal myositis require conservative debridement and antibiotic treatment.

Abdominal infections

Postoperative wound infections, peritonitis, and intra-abdominal and liver abscesses are frequently anaerobic and result from the predominance of anaerobic organisms, particularly *Bacteroides* and *Peptostreptococcus*, in the gastrointestinal tract. Appendicitis, diverticulitis, and perforations of the colon from disease and trauma commonly result in anaerobic infections. *E. coli, Bacteroides, Pepto-*

Table 16-3. Differential diagnosis of gas-forming infections

	Anaerobic cellulitis	Clostridial myonecrosis (gas gangrene)	Infected vascular gangrene	Streptococcal myositis
Organism	*Clostridium;* anaerobes; *E coli; Klebsiella*	*Clostridium*	*Clostridium;* anaerobes; *E. coli; Klebsiella*	*Peptostreptococcus*
Incubation	> 3 days	< 3 days	> 5 days	3-4 days
Onset	Gradual	Sudden	Gradual	Subacute
Pathology	Invasion of connective tissue and not muscle	Invasion of viable muscle	Invasion of necrotic tissue	Invasion of nonviable tissue
Toxemia	Minimal	Severe	Minimal	Late and severe
Gas	Abundant	Slight	Abundant	Moderate
Pain	Slight	Severe	Variable	Severe
Swelling	Slight	Marked	Marked	Marked
Exudate	Slight to moderate	Profuse	Slight	Profuse

streptococcus, and the *Aerobacter-Klebsiella* group are the bacteria most commonly isolated from intra-abdominal abscesses. With careful anaerobic culture techniques, the frequency of anaerobic pathogens approaches 60% to 70%.[3] A "sterile abscess" diagnosed on the basis of negative cultures probably represents an inability to identify anaerobic organisms. Abscesses may occur in a variety of locations, including the subphrenic and intrahepatic areas, interloop regions, and the pelvis. Signs and symptoms of anaerobic abscesses are those of intra-abdominal abscesses and peritonitis in general. The presence of gas in tissues is not specific for anaerobic infections, since some facultative organisms, especially the coliforms, also produce gas.

Anaerobic liver abscesses have been recognized with increasing frequency, and some series have indicated that almost 50% of all liver abscesses are anaerobic in origin.[31] Anaerobic and microaerophilic streptococci, *Bacteroides, Fusobacterium,* and *Actinomyces* have been recovered. Clues to the anaerobic etiology of the infection have included findings similar to other anaerobic infections (foul smell, unique morphology on gram stain, gas production, and lack of growth aerobically).

Anaerobic infections of the gallbladder are not common, yet clostridial organisms can be cultured from the bile in 20% of cases with biliary tract diseases.[17] The rare occurrence of emphysematous cholecystitis is usually caused by clostridial organisms (rarely other anaerobes) in elderly diabetics. Clostridial infections following biliary tract surgery can lead to serious complications, with the infections tending to remain in the subcutaneous tissue about the wound, rarely producing peritonitis. Clostridial sepsis can occur with hemolysis, jaundice, oliguria, and severe toxicity.

Bacteremia

Septicemia is the presence of positive blood cultures with clinically significant findings, whereas bacteremia may occur without signs of infection. *P. acnes* has been the most commonly cultured anaerobe from the blood, with 151 and

264 patients with anaerobic bacteremia demonstrating this organism.[10] Only one of the 151 patients with *P. acnes*, however, demonstrated signs of clinical infection. The clinical importance of anaerobic septicemia has been stressed with particular emphasis on the *Bacteroides* organisms.[12, 23, 40]

Clostridial septicemia most commonly follows septic abortion and is associated with *C. perfringens*. It can also be a complication of clostridial myonecrosis, gallbladder surgery, or bowel tumors.[16] The general findings and modes of therapy are discussed under septic abortion. *Bacteroides* and peptostreptococcal septicemia result from organisms gaining entrance via the bowel, the pharynx, or the pelvis. Foci of infection may arise in the tonsillar region, middle ear, and mastoid, from the prostate and decubitus ulcers, but only rarely from pulmonary lesions. Septicemia may be associated with septic embolization to the lungs, liver, kidneys, and joints. Treatment is directed toward draining the primary focus and the administration of antibiotics.

Superficial infections

The most common superficial skin lesions associated with anaerobic infections include infected pilonidal cysts and perirectal abscesses. Drainage without the use of antibiotics is usually sufficient treatment. Anaerobic streptococci and *Bacteroides* are the most commonly recovered organisms.

Infections following human bites are usually severe and extensive. Severe pain, fever, moderate toxemia, and a wound with progressive necrosis and a purulent foul discharge are typical findings. A mixture of bacteria is present, including spirochetes, anaerobic nonhemolytic streptococci, staphylococci, and *B. melaninogenicus*. Proper initial treatment with penicillin, debridement, and nonclosure of the wound can prevent most infections. With established infections, radical decompression of the tissue planes and penicillin therapy are required.

Meleney's ulcer (progressive bacterial synergistic gangrene) (Fig. 16-3) begins in the skin, often around retention sutures, following drainage of an abdominal abscess, an operation for a purulent infection of the chest, or a traumatic wound. Usually a typical lesion is recognized 1 to 2 weeks after operation. Initially the skin around the wound or retention sutures becomes edematous, erythematous, and painful. As the lesion progresses it enlarges, with the central portion becoming necrotic and ulcerated. The base of the ulcer is dirty with infected granulation tissue, and the edges are undermined. When the lesion is fully developed, three distinct zones can be identified. Peripheral to the gangrenous central ulceration is an elevated tender purplish area surrounded by a 1 to 10 cm region of erythema that fades into normal skin. Burrowing necrotic tracts can extend from the central lesion and result in distant ulcerated areas. The ulcerative process is slowly progressive and can necrose large areas of soft tissue and ultimately cause death if inadequately treated.

Meleney's ulcer is a synergistic infection involving microaerophilic nonhemolytic streptococcus in the spreading periphery of the lesion and *Staphylococcus aureus* in the central ulcerated area. Bacteriologic studies performed in dogs by Meleney demonstrated that neither the *Staphylococcus aureus* nor the microaerophilic nonhemolytic streptococci would cause the lesion when injected separately, but that both were required together in a 50% mixture to duplicate the lesion seen in man.[25] A synergism between *Proteus* or other gram-negative

Fig. 16-3. Progressive bacterial synergistic gangrene (Meleney's ulcer) involving an abdominal operative wound closed with retention sutures. (From Bornstein, D. L., et al.: Medicine 43:207, 1964.)

rods and nonhemolytic microaerophilic streptococcus can also primarily cause this lesion. The lesions are typically painful and tender on palpation. At first systemic manifestations are minimal, but later low-grade fever, anemia, muscle wasting, general debilitation, and marked toxemia develop.

Topical treatment with antibiotics, peroxides, ointments, wet dressings, and limited debridement has not been effective in eradicating this entity. The best treatment includes early, aggressive, and wide excision of the entire gangrenous portion, including the ulcerated base and any sinus tract extensions. Large areas may need debridement to expose viable tissue. Systemic penicillin and a broad-spectrum antibiotic (kanamycin or gentamicin) are given prior to and after operation to limit the severe toxemia that may occur. After excision the wound is left open, and skin grafts are applied when the granulation tissue is favorable.

SUMMARY

It is not generally recognized that anaerobic organisms constitute an important and significant aspect of surgical infections. Recent improvements in anaerobic culture techniques as well as a growing awareness of these organisms on the part of clinicians and microbiologists have resulted in an increased incidence of anaerobic infections reported from a few institutions. *Clostridium*, *Bacteroides*, and *Peptostreptococcus* are the clinically important pathologic

anaerobes. *P. acnes* and *Veillonella* are the nonpathogenic anaerobes that are most frequently recovered from clinical specimens. Most of the anaerobic infections are endogenous in origin because almost all clinically significant organisms can be found normally on the body as commensals. Aside from the generally familiar entities of botulism, tetanus, and gas gangrene, there are many more commonly occurring anaerobic infections. The most frequent of these are brain abscesses, oral infections, putrid lung abscesses, intra-abdominal abscesses following bowel and gynecologic surgery, perirectal and pilonidal cyst infections, puerperal and postabortal infections, and septic thrombophlebitis. Infections that are foul-smelling, produce gas, or follow bowel, gallbladder, or gynecologic operations must be suspected of being anaerobic in origin. Septicemia in association with repeatedly negative blood cultures may be caused by anaerobes. Debridement and drainage constitute the mainstay of treatment. Antibiotics, and in some cases antitoxins, hyperbaric and local oxygen therapy, heparin administration, and vein ligation serve as important adjunctive measures. All anaerobic organisms are sensitive to chloramphenicol and clindamycin, and all but *B. fragilis* are sensitive to penicillin G. Resistance of the anaerobes to tetracycline is increasing. Gram staining of clinical material can provide immediately useful information and assist in the interpretation of culture results. Immediate culturing of clinical material in a prereduced medium will result in the best recovery of anaerobes. The significance of anaerobes must be seriously considered when the use of preoperative bowel "sterilization" and prophylactic antibiotic administration for bowel injuries are discussed. Although anaerobic organisms have been mentioned only infrequently in surgical teaching and in the surgical literature, their importance needs to be stressed in the future.

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17

Perfusion of the extremities*

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EDWARD T. KREMENTZ

The chemotherapy of cancer by regional perfusion was first developed for clinical use by Creech, Krementz, and Ryan of the Tulane University department of surgery in 1957 in an attempt to obtain maximum tumoricidal effects with minimum systemic toxicity.[5, 15] The concept was that if a chemotherapeutic agent could be confined to a tumor-bearing area by establishing a temporary extracorporeal circulation through the major artery and veins supplying the region and by isolating the region by appropriately placed tourniquets, systemic toxicity would be reduced, and the total dose would be limited only by local tissue tolerance.

During the developmental period, techniques for perfusion of most regions of the body were devised, many different histologic types of tumor were treated, and many of the cancericidal drugs available at that time were studied.[3-5] As of December 31, 1973, 925 patients with a wide variety of tumors had undergone perfusion on 1059 occasions. A high but short-term response rate was seen in solid tumors that had been otherwise nonresponsive to systemic chemotherapy. Sustained remissions were most commonly seen in patients with melanoma of the extremities after perfusion with melphalan alone or in combination with thiophosphoramide (thio-tepa). This chapter will be confined to discussion of our experience in the treatment of invasive melanoma of the skin of the extremities by this technique.

Fortuitously, the first patient selected for chemotherapy by regional perfusion had satellitosis of the lower extremity secondary to a previously excised

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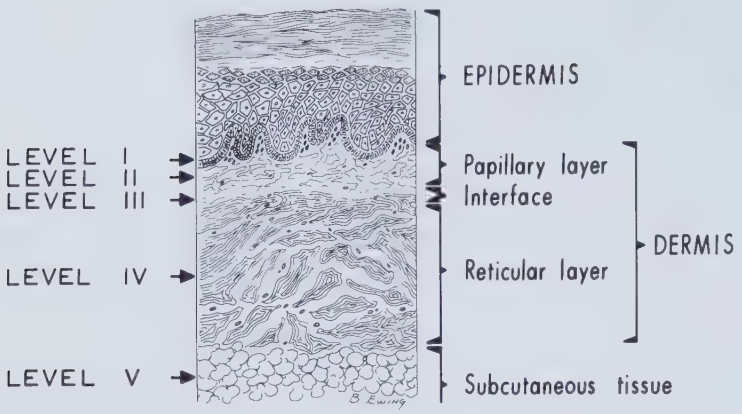
malignant melanoma of the skin of the ankle.[5] The patient experienced a complete remission after femoral perfusion with melphalan, the remission persisting until his death of natural causes 14 years later at the age of 91 years.

The use of chemotherapy by perfusion is indicated in patients both as a curative and a palliative procedure. In the former category the method has been used alone in a few instances in patients with primary disease, some of whom refused excisional surgery or more commonly in those patients with regionally confined but advanced disease such as satellitosis or diffuse subcutaneous metastases. The largest group includes those patients treated by perfusion as an adjunct to conventional surgical excision in stage I and II disease. In a few instances in stage II disease it has been possible to convert the inoperability of the patient to operability. When utilizing this technique for palliation only, it has been possible to save a functional extremity with stage III disease, such as extremities harboring metastases distant from the primary tumor, to relieve pain, to heal ulceration, or to reduce the size of bulky nonresectable tumors confined to the extremity.

PATIENT EVALUATION

The majority of the patients referred to our group have had previous excisional biopsy. At initial consultation a careful history relative to the growth and behavior of the primary lesion is recorded, and the patient is examined for other suspicious pigmented lesions. In our experience, several patients with double primaries have been encountered. The referring physician is requested to forward the slides made from sections of the primary lesion. The sections are reviewed for classification and categorized according to the criteria independently described by Clark et al.[2] and by McGovern[9] to determine if the lesion is malignant lentigo, superficial spreading melanoma, or nodular invasive melanoma. The level of invasion of the skin is also determined (Fig. 17-1). The patient is further evaluated by obtaining a complete history and a physical examination, including studies to determine the presence or absence of metastasis by chest x-ray examination, metastatic series, liver function studies, liver scan, and other tests as indicated. A 24 hr urine sample is analyzed for melanin metabolites.[10] The selection of appropriate treatment is determined on the basis of the clinical stage of disease, the site and level of invasion of the primary tumor, and the patient's age, sex, and general condition, as discussed in the following sections.

Stage I. Stage I lesions are defined as being localized to the primary tumor. Level I and II invasions are treated by wide excision. With deeper levels of invasion in stage I lesions of the thigh, an external iliac perfusion is performed, followed by a groin dissection, including removal of the iliac nodes when enlarged. A wide excision of the tumor site is carried out and repaired with a split-thickness skin graft. When the lesion is at or below the knee, a common femoral perfusion is performed followed by a femoral node dissection and a wide excision of the primary lesion and repair with a split-thickness skin graft. For upper limb stage I lesions, perfusion of levels III, IV, and V is carried out through the first portion of the axillary vessels, followed by an axillary node dissection and a wide excision of the primary lesion. The axillary dissection is performed by dividing the pectoral muscles and removing the lymph nodes



I	All tumor cells are above basement membrane.
II	Cells have broken through basement membrane into papillary dermis.
III	Cells extend through papillary dermis to interface.
IV	Cells extend into reticular dermis.
V	Cells extend into subcutaneous tissue.

Fig. 17-1. Anatomic levels of skin used to determine histologic staging of malignant melanoma.

from the apex of the axilla to the lateral border of the latissimus dorsi. For the past several years suitable patients with stage I lesions have undergone a modified axillary dissection without division of the pectoral muscles. In lesions arising within 15 cm of the groin or axilla, an in-continuity dissection, including the skin and underlying soft tissue with the lymphatics to the regional nodes, is performed.

Stage II. Stage II includes patients with an extension of disease to the intervening tissue between the primary tumor and to the regional nodes or those patients with regional satellitosis. In these patients perfusion is followed by appropriate dissection of regional nodes and a wide excision of metastatic or recurrent disease, particularly if there is a solitary or limited recurrence. With more extensive disease or satellitosis, perfusion alone is performed. Following regression of disease, a second procedure is performed that may include perfusion and/or excision of residual melanoma after a 3- to 6-week interval.

Stage III. Stage III includes patients with distant metastases and those patients with positive iliac nodes from lower extremity primary lesions or extension of disease beyond regional nodes. These patients are treated by perfusion for palliative purposes only and in conjunction with systemic chemotherapy or immunotherapy.

TECHNIQUE

A Sigma motor pump or a rotary-head pump is used to maintain extracorporeal circulation (Fig. 17-2) through a sterile disposable oxygenator (Travenol 1-LF Miniprime). A Marchand-Creech or disposable venous in-line heat exchanger is incorporated into the system to maintain the perfusate tem-

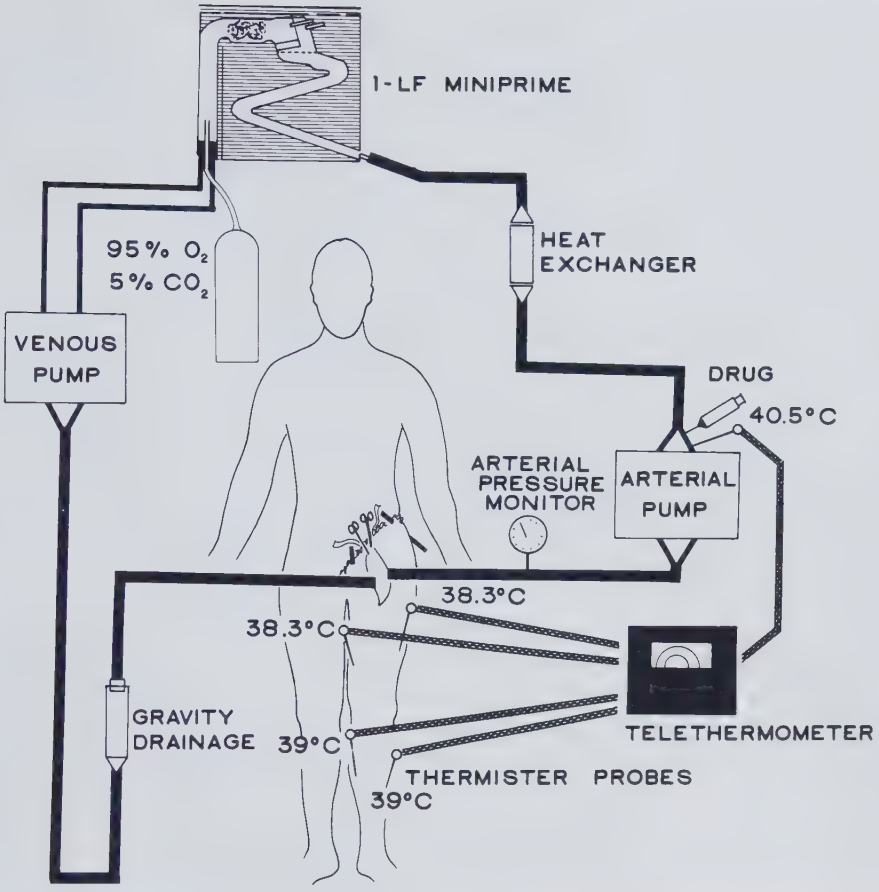


Fig. 17-2. Schematic diagram of perfusion circuit and equipment for common femoral perfusion.

perature at 40° C. The pump is primed with 300 ml Ringer's lactate and 250 ml whole fresh blood. A commercial in-line 70 micropore filter is used to filter the priming blood. A mixture of 95% oxygen and 5% carbon dioxide is bubbled through the oxygenator at 3 L/min. Venous blood flows by gravity to a vented collection reservoir and is pumped from the reservoir to the oxygenator. The rate of arterial flow is regulated by the volume of venous return and by the pressure in the arterial line, which is monitored between the pump head and the patient and maintained at or slightly below the patient's systolic blood pressure to prevent loss of drug from the circuit. Flow rates for common femoral or external iliac perfusion are maintained between 200 and 400 ml/min, whereas flow rates for axillary perfusion are usually maintained between 150 and 250 ml/min.

The patient is heparinized systemically with 150 units/kg body weight. Catheters are placed in the appropriate vessels, and a tourniquet is applied to obtain maximum isolation of the area to be perfused. The distribution of the flow resulting from the position of the catheter in the artery is ascertained by

Table 17-1. Safe range of drug dosage for perfusion of extremities (mg/kg body weight)

Drug	Upper extremity	Lower extremity
Melphalan	0.5 -0.9	1.0-1.4
TSPA	0.5 -0.9	1.0-1.4
Melphalan and TSPA	0.4 -0.6 and 0.1-0.3	0.7-0.9 and 0.3-0.5
HN2	0.15-0.35	0.4-0.55

introducing 3 ml fluorescein (Fluorescite) into the arterial system; the limb is then observed in a darkened room under Wood's light. Adjustments can be made to correct "hot spots," inadequate coverage of the skin area, or escape above the tourniquet. If there is any question with regard to distribution, an arteriogram can be performed. To achieve and maintain optimum temperature in the limb (ideally 39° C), it is wrapped with an external heating device and the temperature of the perfusate is maintained at 40.5° C throughout the procedure. Limb temperatures are monitored by thermistor probes placed deep subcutaneously at four sites over the limb.

When the limb temperature has reached at least 37° C, the drug of choice is injected into the arterial line in equal divided doses. The rapidly acting agents, e.g., nitrogen mustard (HN2) and actinomycin D, are given in small increments (no more than 3 mg HN2 at one time) every 2 min and circulated for 10 to 15 min following the last dose. Longer acting agents, e.g., melphalan and TSPA, are given in three to four increments at 4 min intervals and the perfusion continued for 45 min. (Appropriate dosages for extremity perfusion are listed in Table 17-1.) At the completion of the procedure the extremity is washed out with 250 ml of dextran followed by 250 ml of whole blood. The catheters are withdrawn and the vessels repaired. Protamine sulfate is then administered to counteract the heparin effect if excision is to follow. Appropriate excisional surgery is then carried out.

OPERATIVE PROCEDURES

Upper extremity. For lesions located distal to the shoulder, the first portion of the axillary artery and vein are cannulated through the deltopectoral groove. A tourniquet is placed around the base of the forequarter and held in place with Steinmann pins placed through the skin and subcutaneous tissue. After the perfusion is completed, in patients with subungual or distal phalangeal lesions a minor amputation is carried out. With lesions in other regions, a wide excision with skin graft is performed. In a few cases primary closure is performed if the width of excision is not compromised. In stage I disease in women, if confirmed by open exploration of the axilla at the time of perfusion, axillary node dissection is not performed. If the lesion is located on the shoulder, the perfusion is carried out through the subclavian vessels by removing the first third of the clavicle in order to place the cannulas in the subclavian vessels. Following this, axillary node dissection and a wide excision of the primary lesion are carried out. Alternatively, the subclavian vessels are occluded and a retrograde perfusion is performed through the brachial vessels. In addition to the wide

excision and axillary node dissection, in more proximal lesions a supraclavicular node dissection is performed when indicated.

Lower extremity. If the lesion is in or below the distal thigh, perfusion is carried out through the common femoral vessels. If the lesion lies in the proximal thigh, an external iliac perfusion is performed. If the external iliac nodes are positive, the nodes may be swept off the iliac vessels and a perfusion then performed, or a common iliac perfusion may be performed. However, the latter requires an abdominal or transperitoneal approach. Patients with lesions of the iliac nodes require additional immunotherapy or systemic chemotherapy for curative treatment, as they usually have undetected systemic metastases. Following femoral node dissection, the proximal sartorius muscle is transplanted medially to cover and protect the femoral vessels. If an iliac perfusion is performed, the distal iliac and obturator nodes are removed together with the inguinal and femoral nodes; usually the inguinal ligament is preserved.

In lower extremity perfusions an Esmarch bandage is placed around the base of the extremity and held in place by Steinmann pins, one placed subcutaneously through the skin and subcutaneous tissue in the lower quadrant just lateral to the midline and the other pin placed posteriorly and inferiorly from the anterosuperior iliac spine.

In those cases where the primary lesion lies close to the axilla or groin, an in-continuity dissection is carried out on the skin and subcutaneous tissue between the primary and regional nodes. Thin skin flaps have been avoided, and with the utilization of a suction catheter for drainage, ischemic necrosis of the skin flaps is uncommon. An attempt to preserve the deep fascia intact has been made on the basis of the observations of Olsen[12] of Denmark and Bodenham[1] of Great Britain, whose results have suggested that this structure acts as a protective anatomic barrier to metastatic spread from the primary site.

CLINICAL MATERIAL

From June, 1957, through December 31, 1973, 629 patients with melanoma have been treated by regional perfusion with chemotherapy on 745 occasions. A total of 582 patients had invasive melanoma of the extremities; of these, 204 were on the upper extremity and 378 on the lower extremity. There were 29 patients with melanoma of the head and neck, 12 with pelvic melanoma, 4 with breast melanoma, and 2 with brain lesions that were also treated by perfusion. The responses in the patients whose melanoma did not involve an extremity were of a limited nature, so that chemotherapy by perfusion at the present time is restricted to these sites for palliation only. The presentation of long-term survival results will be primarily concerned with the 421 patients with stage I and II disease. Of these, 198 patients had localized stage I disease and 223 had regional involvement (stage II disease). There were 111 patients with stage III disease, including those with involvement of the iliac nodes in the case of lower extremity lesions or patients with any involvement outside of the extremity. Thirty-eight patients were excluded from the long-term survival results because the period of follow-up was less than 1 year. These patients were treated in 1973 and will not be added to the survival studies until 1 year has passed. As there have only been nine hospital deaths in the entire series, and none of the recent patients have been lost to follow-up, the

Table 17-2. Cumulative survival rates in 421 patients with malignant melanoma of the extremities by stage of disease treated with chemotherapy by perfusion in addition to standard surgical procedures

Year	Stage I			Stage II			Stages I and II		
	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	198	3	98.5	223	45	79.8	421	48	88.5
2	178	8	94.0	165	45	58.0	343	53	74.8
3	159	7	89.8	109	16	49.5	268	23	68.4
4	136	5	86.2	84	7	45.4	220	12	64.6
5	124	5	82.6	70	6	41.5	194	11	60.9
6	102	5	78.5	59	3	37.4	161	8	57.8
7	85	1	77.7	53	1	36.7	138	2	56.9
8	65	1	76.2	46	1	35.9	111	2	55.8
9	57	0	76.2	45	0	35.9	102	0	55.8
10	45	0	76.2	27	0	35.9	72	0	55.8
11	35	0	76.2	21	0	35.9	56	0	55.8
12	25	0	76.2	17	0	35.9	42	0	55.8
13	13	0	76.2	12	0	35.9	25	0	55.8
14	4	0	76.2	7	1	30.8	11	1	50.7
15	0	0		3	0	30.8	3	0	50.7

percentage of survivors who are considered cured will not be significantly altered. Two patients with double primary lesions, six that died from other causes, and four that were lost to follow-up prior to first-year evaluation were also excluded. An additional 19 patients who died of other causes and one who was lost to follow-up after the first year were excluded the year their status ceased to be evaluated.

Of the 421 patients, there were 260 women and 161 men in an age range from 17 to 90 years. There were 405 whites and 12 blacks in the group. Of the 582 perfusions for melanoma of the extremities, 496 patients underwent perfusion once, 62 twice, 17 three times, 5 four times, and 2 five times. The majority of patients had involvement of the distal portion of the limb when the upper limbs were affected; the upper arm was involved in 43 patients. In the lower extremity cases, the leg was most commonly involved, accounting for 159 cases, followed by involvement of the foot and thigh. There were eight subungual lesions in the upper extremity and nine in the lower extremity. In 34 instances in the upper extremity and six instances in the lower extremity, patients presented controlled primary lesions on the trunk that were metastatic to the axilla or groin; in these circumstances the patient was treated by perfusion and regional node dissection. In addition, there were 13 patients with an unknown primary lesion that appeared as a metastatic lesion to the axilla in five instances and to the groin in five instances. Additionally, five patients had lesions in the face or scalp that were controlled and then had metastasized to an extremity; these patients were treated by perfusion and excision.

Melphalan was used most frequently, being employed in 472 perfusions. A combination of melphalan and TSPA was used 171 times. HN2 was used on 39 occasions, usually in patients being treated by a second perfusion after a previous unsuccessful melphalan perfusion. Other drugs were used, including actinomycin D, Mitomycin C, and colchicine alone or in combinations of the above, on 13 occasions.

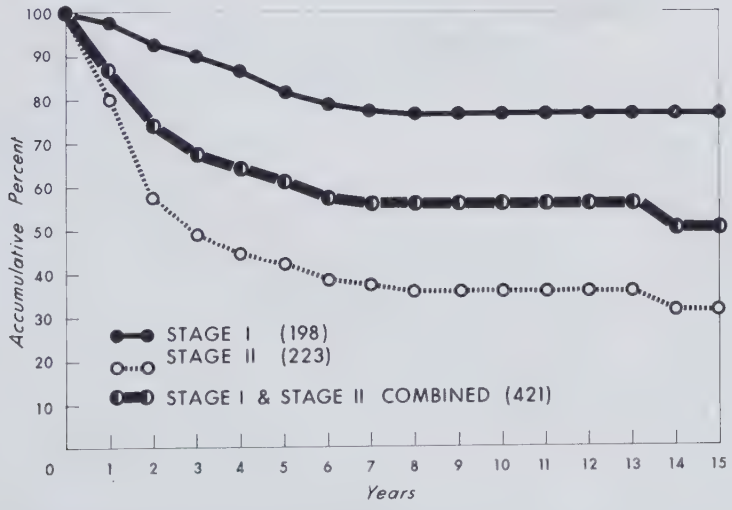


Fig. 17-3. Cumulative survival curve by stage of disease for 421 patients with malignant melanoma of extremities treated with chemotherapy by perfusion and/or with surgical excision.

RESULTS

The long-term survival results are presented as the cumulative survival rates. These are determined by the statistical method used in the life survival rate table follow-up approach presented by Remington and Schork[13] In this method the cumulative survival in each year is equal to the product of the yearly survival rates for all the years up to and including that year.

Table 17-3. Cumulative survival rates of patients with stage I malignant melanoma of upper extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection

	Male			Female		
Year	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	37	0	100.0	26	0	100.0
2	37	3	91.8	22	0	100.0
3	32	1	89.0	21	0	100.0
4	26	2	82.0	18	1	94.4
5	23	0	82.0	15	0	94.4
6	19	1	78.0	14	1	87.0
7	14	0	78.0	12	0	87.0
8	7	0	78.0	9	0	87.0
9	7	0	78.0	7	0	87.0
10	5	0	78.0	7	0	87.0
11	2	0	78.0	5	0	87.0
12	2	0	78.0	2	0	87.0

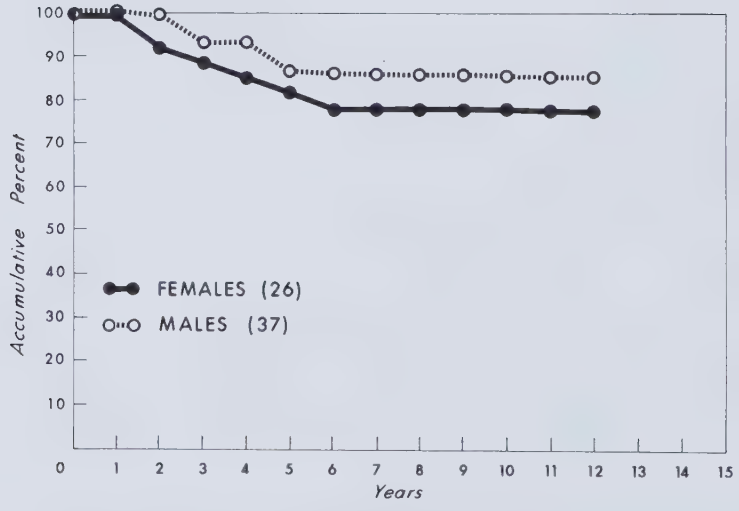


Fig. 17-4. Cumulative survival curve by sex for 63 patients with stage I malignant melanoma of upper extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection.

Combined stage I and II cumulative survival rates. There were 421 stage I and II lesions, i.e., 198 patients with stage I and 223 patients with stage II disease. The results of treatment by perfusion and varying types of surgical excision as indicated in the description of treatment are shown in Table 17-2 and Fig. 17-3. The cumulative survival for stage I patients after 5 years is 82.6% and for stage II patients is 41.5%. After 10 years the percent survival is 76.2%

Text continued on p. 440.

Table 17-4. Cumulative survival rates of patients with stage I malignant melanoma of the lower extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection

	Male			Female		
Year	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	26	0	100.0	74	1	98.6
2	25	0	100.0	67	3	94.2
3	23	1	95.6	61	3	89.5
4	21	2	86.5	52	0	89.5
5	18	3	72.0	49	2	86.0
6	14	0	72.0	38	2	81.7
7	11	1	65.5	32	0	81.7
8	7	1	56.0	26	0	81.7
9	6	0	56.0	22	0	81.7
10	3	0	56.0	16	0	81.7
11	2	0	56.0	13	0	81.7
12	2	0	56.0	8	0	81.7
13	1	0	56.0	6	0	81.7

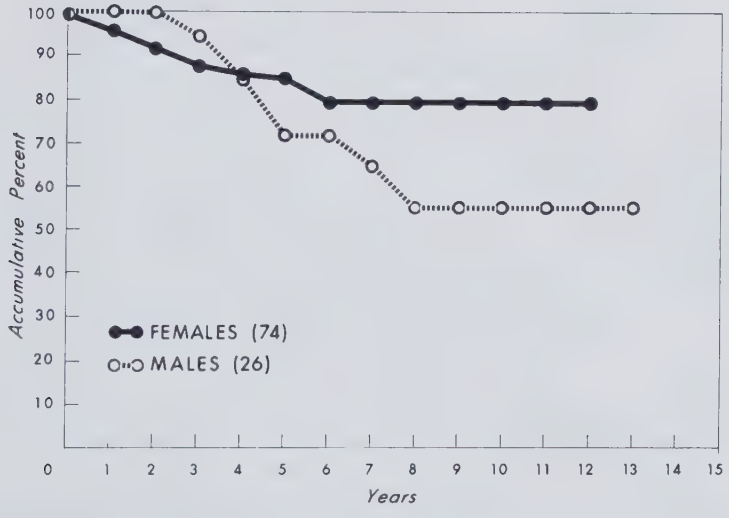


Fig. 17-5. Cumulative survival curve by sex for 100 patients with stage I malignant melanoma of lower extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection.

Table 17-5. Cumulative survival rates in patients with stage I malignant melanoma treated with chemotherapy by perfusion, wide excision and *no* regional lymph node dissection

Year	Upper extremity			Lower extremity		
	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	16	1	93.0	19	1	94.7
2	10	0	93.0	17	2	83.6
3	10	1	83.7	12	1	76.9
4	9	0	83.7	10	0	76.9
5	9	0	83.7	10	0	76.9
6	7	0	83.7	10	1	69.0
7	7	0	83.7	9	0	69.0
8	7	0	83.7	9	0	69.0
9	6	0	83.7	9	0	69.0
10	5	0	83.7	9	0	69.0
11	4	0	83.7	9	0	69.0
12	4	0	83.7	7	0	69.0
13	3	0	83.7	3	0	69.0
14	1	0	83.7	3	0	69.0

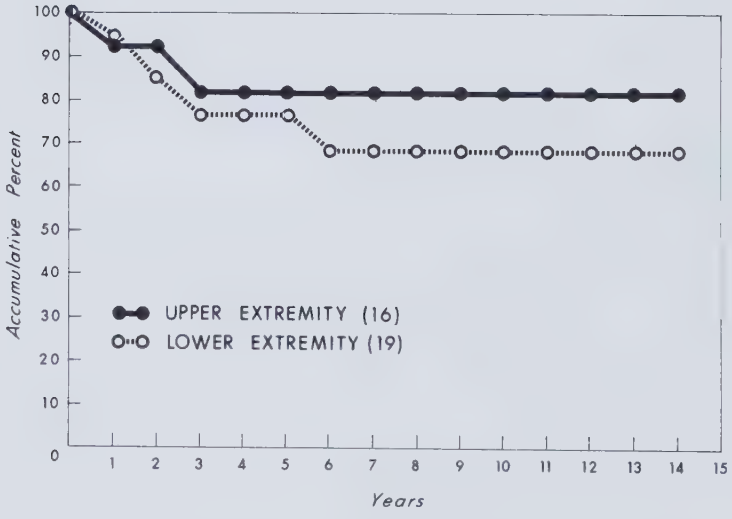


Fig. 17-6. Cumulative survival curve by extremity for 35 patients with stage I malignant melanoma treated with chemotherapy by perfusion, wide excision, and *no* regional lymph node dissection.

Table 17-6. Cumulative survival rates of patients with stage II malignant melanoma of upper extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection (node involvement with or without cutaneous disease)

Year	Male			Female		
	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	39	7	82.0	19	7	63.0
2	28	5	67.0	11	1	57.0
3	21	5	51.0	9	0	57.0
4	15	1	48.0	9	0	57.0
5	12	2	40.0	9	0	57.0
6	9	0	40.0	8	0	57.0
7	9	0	40.0	7	0	57.0
8	7	0	40.0	7	0	57.0
9	6	0	40.0	7	0	57.0
10	3	0	40.0	3	0	57.0
11	1	0	40.0	2	0	57.0
12	0	0	—	2	0	57.0
13	0	0	—	2	0	57.0
14	0	0	—	1	0	57.0
15	0	0	—	1	0	57.0

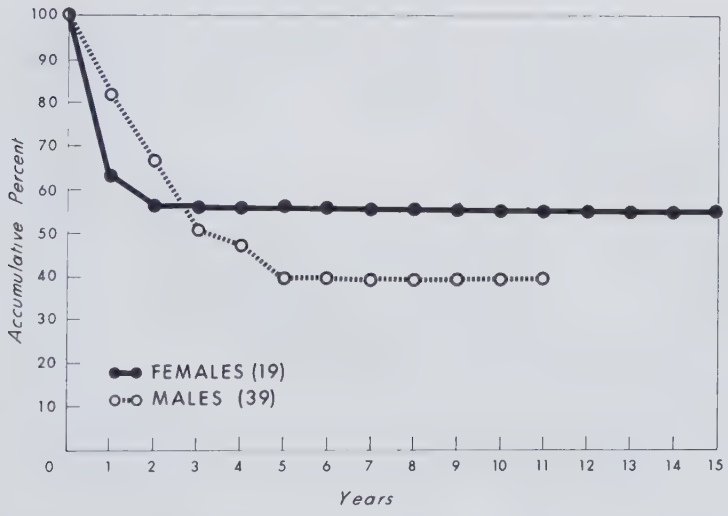


Fig. 17-7. Cumulative survival curve by sex for 58 patients with stage II malignant melanoma, having regional lymph node involvement with or without cutaneous metastasis of upper extremities treated with chemotherapy by perfusion, wide excision of primary lesion, lymph node dissection, and excision of metastasis if possible.

Table 17-7. Cumulative survival rates of patients with stage II malignant melanoma of lower extremities treated with chemotherapy by perfusion, wide excision, and regional lymph node dissection (node involvement with or without cutaneous disease)

Year	Male			Female		
	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	46	10	78.0	58	14	76.0
2	35	14	47.0	42	11	56.0
3	20	4	38.0	28	3	50.0
4	14	1	35.0	23	1	47.8
5	13	3	30.0	18	0	47.8
6	10	1	27.0	17	1	42.0
7	9	0	27.0	14	0	42.0
8	9	0	27.0	11	1	38.0
9	8	0	27.0	12	0	38.0
10	7	0	27.0	6	0	38.0
11	7	0	27.0	4	0	38.0
12	7	0	27.0	4	0	38.0
13	4	0	27.0	2	0	38.0
14	1	1	—	2	0	38.0
15	0	0	—	2	0	38.0

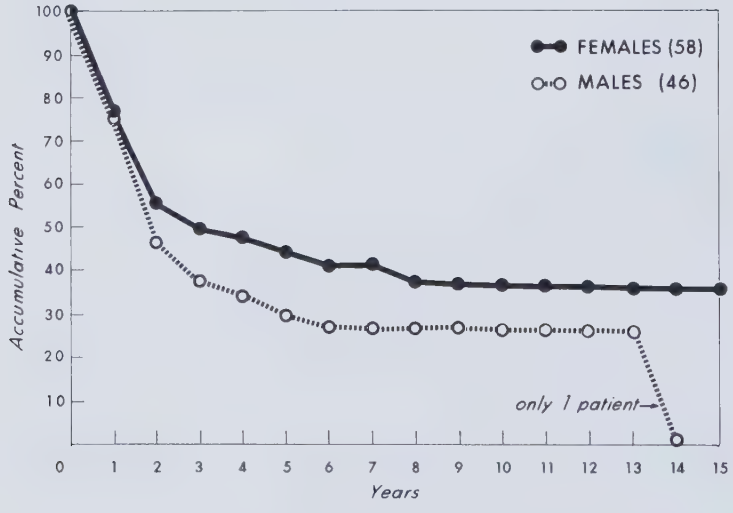


Fig. 17-8. Cumulative survival curve by sex for 104 patients with stage II malignant melanoma, having regional lymph node involvement with or without cutaneous metastasis of lower extremities treated with chemotherapy by perfusion, wide excision of primary lesion, lymph node dissection, and excision of metastasis if possible.

Table 17-8. Cumulative survival rates of patients with stage II malignant melanoma of lower extremities treated with chemotherapy by perfusion, wide excision, regional lymph node dissection, and excision of recurrence if indicated (no node involvement but with cutaneous or subcutaneous metastasis)

	Male			Female		
Year	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	10	1	90.0	43	5	84.0
2	7	1	77.0	37	13	54.5
3	6	0	77.0	20	5	41.0
4	5	2	46.0	13	2	34.7
5	3	1	30.6	10	0	34.7
6	2	0	30.6	9	1	30.8
7	2	0	30.6	8	0	30.8
8	1	0	30.6	8	0	30.8
9	1	0	30.6	8	0	30.8
10	1	0	30.6	6	0	30.8
11	1	0	30.6	6	0	30.8
12	0	0	—	3	0	30.8
13	0	0	—	3	0	30.8
14	0	0	—	3	0	30.8
15	0	0	—	0	0	30.8

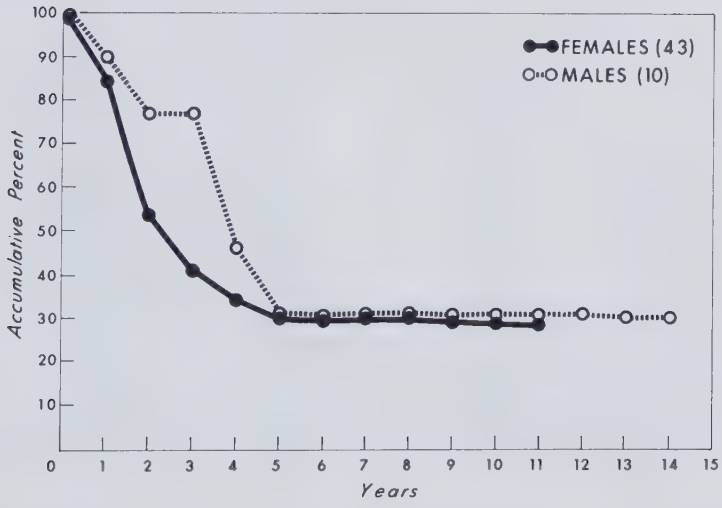


Fig. 17-9. Cumulative survival curve by sex for 53 patients with stage II malignant melanoma having no regional lymph node involvement with dermal or subcutaneous metastasis of lower extremities treated by perfusion and excision of metastasis when indicated.

and 35.9%, respectively. It is of some interest that after the eighth year in stage I patients, the salvage curve remains flat; this is essentially true for the stage II patients from the eighth through the twelfth year, when one late death from disease occurred. When both stage I and II patients are combined, salvage rates at 5 and 10 years are 60.9% and 55.8%, respectively.

Cumulative survival rates for stage I patients. The stage I patients have been separated into cohorts of upper and lower limb disease with regional node dissection and according to sex. In Table 17-3 and Fig. 17-4 the salvage rates for 26 females and 37 males with upper extremity disease and regional node dissection are depicted. After 5 years the salvage rate of 82% is seen in the males and 94.4% in the females. There is no statistically significantly difference in the salvage between sexes among these two groups. In Table 17-4 and Fig. 17-5, statistics for the patients with stage I disease treated by regional lymph node dissection in the lower extremities are presented. There were 74 females and 26 males in this group. After 5 years there is some difference in salvage rate, 72% in males as compared to 86% in females. After 10 years the difference is more apparent, with an 81.7% salvage in the females as compared with 56% salvage in the males. In Figs. 17-4 and 17-5, after the fifth year in the former and the eighth year in the latter, the curves remain flat. Additionally, among the stage I patients, there were 35 patients who had no regional lymph node dissection and were treated with perfusion and wide excision only (Table 17-5 and Fig. 17-6). The lymph node dissections were not carried out in these cases (1) because of severe obesity with anticipated problems in wound healing following node dissection; (2) because of medical contraindications to more extensive surgery, e.g., coronary disease; and (3) because in recent years the good salvage rates in upper extremity lesions, particularly in females, has eliminated the practice of node dissection.

Cumulative survival rates for stage II patients. The study of stage II patients included 223 individuals. The patients have been divided into two groups: (1) patients with node involvement with or without dermal or subcutaneous metastasis and (2) patients with no node involvement with dermal or subcutaneous metastasis. These patients were then evaluated as to survival according to site and sex.

There were 58 patients, 19 females and 39 males, in the subgroup of stage II patients with node involvement (Table 17-6 and Fig. 17-7) and an upper extremity primary lesion. Because of the interesting slope of the curves, suggesting that most recurrences occur earlier in females, statistical analysis was performed after 2 years and showed that there is no significant difference in survival rates. Analysis after the 6-year period following the point which the survival curves intersect showed no significant difference.

The stage II patients with node involvement and lower extremity disease includes a total of 104 (58 females and 46 males) individuals (Table 17-7 and Fig. 17-8). Analysis of this group after 5 years shows no statistical difference between the sexes with regard to cumulative survival.

Of the 61 stage II patients with dermal or subcutaneous metastasis and no nodal involvement, 48 were female and 13 were male. There were 53 patients with lower extremity disease. Of these, 43 were female and 10 were male (Table

Table 17-9. Cumulative survival rates of patients with stage II malignant melanoma of upper extremities treated with chemotherapy by perfusion, wide excision, regional lymph node dissection, and excision of recurrence if indicated (no node involvement but with cutaneous or subcutaneous metastasis)

Year	Male			Female		
	No. of patients	Dead	Cumulative % survival	No. of patients	Dead	Cumulative % survival
1	3	0	100.0	5	1	80.0
2	2	0	100.0	3	0	80.0
3	2	0	100.0	3	0	80.0
4	2	0	100.0	3	0	80.0
5	2	0	100.0	3	0	80.0
6	2	0	100.0	2	0	80.0
7	2	1	50.0	2	0	80.0
8	1	0	50.0	2	0	80.0
9	1	0	50.0	2	0	80.0
10	0	0	—	1	0	80.0
11	0	0	—	1	0	80.0
12	0	0	—	1	0	80.0
13	0	0	—	1	0	80.0
14	0	0	—	1	0	80.0
15	0	0	—	0	0	80.0

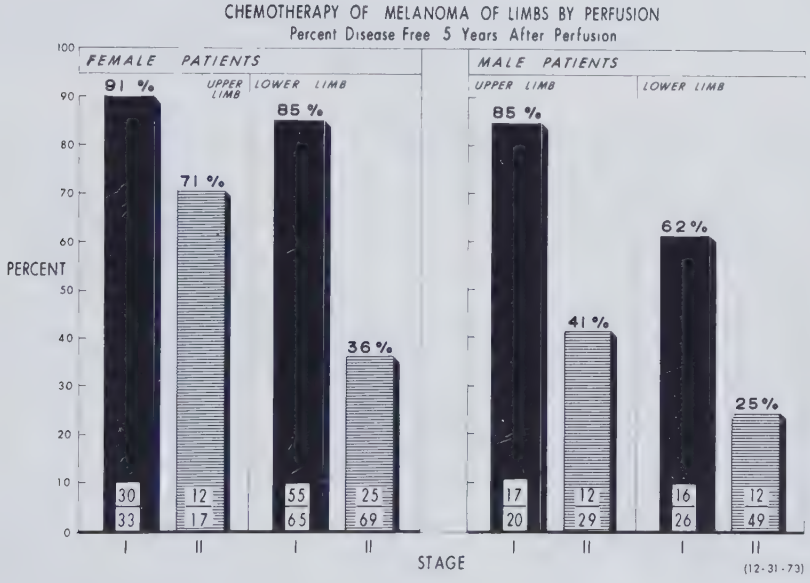


Fig. 17-10. Five-year direct survival rate for determinate cases after chemotherapy by perfusion for melanoma of limbs and additional excisional surgery according to stage, sex, and sites.

17-8 and Fig. 17-9). There were only 5 females and 3 males with upper extremity lesions, as shown in Table 17-9.

These stage II patients would be considered candidates for amputation at other medical centers.

As can be seen in Tables 17-8 and 17-9, this form of disease is rarely seen in upper extremities of either sex or in lower extremities of males. In the cumulative survival rates of males and females with lower extremity disease, there is no difference. Occasionally multiple perfusions are required to control the disease in patients with regional recurrence, i.e., dermal or subcutaneous metastasis.

Utilizing another method of analyzing results, Fig. 17-10, a bar graph, has been prepared to show the direct survival at 5 years following chemotherapy by perfusion and the additional surgery as indicated previously for males and females with stage I and II disease according to site. The direct survival rates include those patients who are free of disease as determined by clinical and laboratory examination. A certain number of highly significant ($p < 0.001$) observations can be made. In addition to the observations presented on the bar graph according to cohort, analysis has been carried out showing that all females do better than all males by a comparison of 67% to 46%, all stage I patients do better than all stage II patients by 82% to 37%, and all patients with upper limb lesions do better than all those with involvement of the lower limbs, 71% as compared to 52%. In addition, the upper limb stage II females do better than the lower limb stage II females, 69% as compared to 38%. Utilizing the same direct survival rates after 5 years with determinate cases, some further observations can be made regarding stage II disease (Table 17-10). Two groups that have done extremely well are those with solitary cutaneous or subcutaneous metastasis, presenting 62% and 76% 5-year salvage rates, respectively. These results almost approach the results of stage I disease. The patient with an intact primary lesion and regional metastases does not do as well. Those with extensive

Table 17-10. Results of chemotherapy by perfusion of malignant melanoma of limb

Special categories	Total determinate cases 5 yr after perfusion		
	No. of patients	Disease free	%
Stage I			
Invasive melanoma	152	119	78
Stage II			
Previously untreated primary lesion with regional metastases	29	10	34
Solitary cutaneous or subcutaneous metastases	13	8	62
Solitary regional node	25	19	76
Extensive regional metastases	39	7	17
Primary site unknown—regional limb disease (nodes, skin, bone)	11	5	45
Satellitosis (upper and lower limb)	45	12	26
Previously with no node involvement	27	7	26
Previously with node involvement	18	5	27

regional metastases, including subcutaneous and/or lymph node involvement, do poorly, with a 17% 5-year direct salvage rate. Those patients in whom the primary lesion site is unknown with regional limb disease treated by perfusion have a 45% survival among the relatively small group of 11 patients. The patients with satellitosis, which represents an interesting aspect of melanoma, have shown a 26% 5-year salvage rate following one or more perfusions with melphalan or HN2 (in the case of second or third repeat perfusions). This entity almost always occurs on the lower extremity and was present in 43 patients with lower limb involvement and in two patients with upper limb involvement. The presence or absence of previous node involvement did not seem to influence the salvage rate appreciably in these relatively small samples. Table 17-11 shows the results in those patients with lower limb satellitosis in addition to the 10 of 43 patients treated more than 5 years ago who are free of disease. An additional seven patients without node involvement at the original operation had local control of disease for 2 to 4 years, but subsequently died of disease, with the exception of one patient who is still alive but who has had multiple recurrences over a 15-year period.

Table 17-11. Outcomes in patients treated by perfusion of lower limbs for satellitosis developing after conventional surgical treatment (43 patients treated 5 years ago or more)

Positive regional node involvement (26 patients)				Negative regional node involvement (17 patients)			
Response	No. of patients	Years controlled	Years survived	Response	No. of patients	Years controlled	Years survived
None	13	0		None	8	0	
Complete remission	6	5-15	5-15	Complete remission	4	5-15	5-15
Temporary	1	1	15	Temporary	1	4	6
remission (7)	1	4	6	remission (5)	1	3	6
	1	2	3*		1	3	4*
	1	1	4		1	2	8
	3	1	2-4		1	1	2

*Died of other causes.

Table 17-12. Chemotherapy of melanoma of the limb by perfusion: results of treatment in stage III disease

	Primary lesion elsewhere and metastases to limb		Primary lesion in limb			
			Iliac node involvement		Systemic metastases	
Year	No. of patients	Disease free	No. of patients	Disease free	No. of patients	Disease free
1	30	6	27	3	41	3
2	30	5	24	2	41	2
3	29	3	24	2	36	1
4	24	2	20	1	33	1
5	23	2	16	0	31	1

There were 98 stage III determinate cases: 30 with the primary lesions elsewhere and metastases to the limb, 27 with primary lesions in the limb and iliac node involvement, and 41 with recurrence of lesions in the limb and systemic metastases (Table 17-12). As can be seen, the number of disease-free patients in these various categories afer 1 year is relatively small and drops off rapidly. On the other hand, in approximately half of the patients, objective responses were seen following perfusion, and good palliation was achieved on a temporary basis.

Table 17-13. Major complications following chemotherapy by perfusion, node dissection, and/or wide excision and skin graft*

Complication	Number
Wound	
Infection	38
Bleeding	13
Seroma	13
Dehiscence with secondary closure	10
Infection with dehiscence	10
Ischemic necrosis	7
	91
Limb (other than wound itself)	
Edema (severe and/or persistent)	48
Nerve and muscle damage†	27
Thrombophlebitis	19
Thromboses‡	
Arterial	6
Venous	4
Complete loss of toenails	1
	105
Systemic	
Leukopenia	
Under 2000/mm^3	32
Under 1000/mm^3	19
Alopecia	14
Pulmonary involvement (atelectasis, pneumonia, etc.)	12
Genitourinary tract infection	8
Pulmonary emboli	3
Cardiac diseases	6
Stomatitis	3
Severe nausea, vomiting, and diarrhea	3
Septicemia	1
	101
Deaths	
Agranulocytosis with septicemia	6
Myocardial infarction	1
Congestive heart failure	1
Cause undetermined	1
	9

*Complications occurred in 196 of 695 perfusions.
†1 required amputation.
‡3 required amputation.

COMPLICATIONS AND DEATHS

Of the 695 perfusions done, 196 complications were encountered (Table 17-13). Of these, nine resulted in death. Six patients died early in the series. Only one postoperative death has occurred since 1966, this resulting from myocardial infarction. Systemic complications from chemotherapy consisted of leukopenia with a white blood count under 2000/mm^3 in 32 patients and under 1000/mm^3 in 19 patients. Severe alopecia occurred in 14 patients; 10 patients had pulmonary complications such as atelectasis and pneumonia; and three had pulmonary emboli. Miscellaneous complications included loss of nails, which, as in the case of alopecia and leukopenia, can be expected when perfusion is done as part of a procedure. Other complications, as listed in Table 17-13, are those generally encountered with any major surgical procedure.

The number of complications is acceptable when one considers that this procedure involves the intra-arterial use of highly toxic drugs, extracorporeal circulation, and radical excisional surgery. The large number of complications early in the experience must be attributed to the developmental process involved with any new procedure.

DISCUSSION

The observations of Clark[2] and McGovern[9] in the last several years have been of great help in clarifying the clinicopathologic categorization of melanoma. Also, by correlating the prognosis with the level of skin invasion, it has been possible to select the most appropriate therapeutic procedure. Thus for patients with stage I malignant lentigo involving levels I, II, and III or superficial spreading melanoma of levels I and II, local excisional surgery is all that is required. Our experience with approximately 100 patients treated in this fashion over the last 6 years has been entirely satisfactory, providing the primary lesion can be carefully studied by serial sections performed by a knowledgeable pathologist. The nodular invasive melanoma is almost never diagnosed with less than level III invasion.

The adjunctive use of chemotherapy by perfusion in melanoma of the limbs has proved to be an important advance in treatment. The data that has been presented in the treatment of stage I invasive melanoma is sufficiently impressive when compared to standard surgical therapy to warrant its continued use in the management of this disease. In stage II disease in certain specific categories, such as in those patients with single regional lymph node invasion or with solitary regional recurrence, the combination of chemotherapy by perfusion and excision has proved to produce results comparable with those obtained in stage I lesions. In the patient with the primary lesion intact and multiple metastasis, a 5-year salvage rate of approximately 35% is observed. In the special category with satellitosis of the limbs, this treatment, now with a 15-year follow-up, produces a 5-year control rate of approximately 25%. Prior to the use of chemotherapy by perfusion, surgical excision by strip excision only produced isolated cures. In our experience, the most effective systemic chemotherapy, the use of a combination of imidazole carboxamide, chloroethyl cyclohexyl nitrosourea (CCNU), and vincristine, will only produce complete remission in approximately 5% of the patients. Immunotherapy by injection of bacillus Calmette-Guerin (BCG) into the satellites has proved effective for the treatment

of individual satellites, but only a few patients show a systemic response of disease in other metastases or satellites. In our own experience, this has been confined to 3 of 30 patients treated; only one of these patients experienced a persistence of response for even 3 years. Consequently, chemotherapy by perfusion seems to be the most effective method in the control of satellitosis of the extremities currently available. (In those patients with stage I disease treated with perfusion, satellitosis has developed as a late recurrence in about 10% of our patients.)

When surgery alone, i.e., excision and node dissection, is used to control melanoma, the conventional rate of recurrence with satellitosis approximates 20%. In patients with stage II disease with multiple or extensive regional metastasis who have a poor prognosis, this method produces some salvage but by no means adequate cure rates. Investigations aimed at improving these results continue. If the patient is immunocompetent as determined by a variety of parameters, autoimmunization with irradiated autologous tumor cells and BCG, which is under study, may be considered; nonspecific immunotherapy with biweekly BCG by the tine plate method is also being evaluated. In patients who are judged immunologically incompetent, further systemic adjunctive chemotherapy is indicated.

As a result of adjunctive chemotherapy and a better understanding of the behavior of malignant melanoma, an important advance in the treatment of melanoma of the extremities has been made; this has been the avoidance of major amputations for extremity melanoma except in very unusual circumstances.

The results obtained with chemotherapy by perfusion have been duplicated in a number of centers, but unfortunately continued experience with the method using an adequate sample of clinical material is necessary to achieve good results with minimal complications. The combination of extracorporeal circulation, regional perfusion techniques, and radical surgery carries certain complications, and complete familiarity with these techniques is required to produce acceptable results. Consequently, these techniques are best performed in well-equipped and staffed medical centers.

SUMMARY

The rationale involved, a brief description of technique, an enumeration of complications, and the results of chemotherapy by isolated regional perfusion and surgical excision in the treatment of invasive malignant melanoma of the extremities have been presented. An evaluation by the cumulative life table survival curve method of 421 patients with stage I and II disease has been given. The overall cumulative survival at 15 years is 76.2% in stage I disease and 30.8% in stage II disease. In those patients with metastatic disease in the extremity alone, it has been noted that a useful extremity was saved in 61 patients with a 10-year cumulative survival of 30% among patients having involvement of the lower extremities.

It is therefore concluded that the procedure of chemotherapy by perfusion can be added to standard surgical treatment with very little increased morbidity or mortality.

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18

Surgical implications of prostaglandins

BERNARD M. JAFFE

In the past 5 years there has been an extraordinary flurry of interest in the prostaglandins. This rise of prostaglandin research alone would justify the inclusion of this chapter in a text on advances in surgery. However, as concepts of the importance of prostaglandins become clearer, their relevance to the practice of surgery becomes more pronounced. These implications take two forms, i.e., the pharmacologic use of prostaglandins as therapeutic agents and the understanding of their role in the pathophysiology of surgical diseases. Although clinical therapeutic evaluation of these compounds is still in the very preliminary stages, this chapter will attempt to describe the potential ways in which prostaglandins may influence the practice of surgery.

GENERAL INFORMATION

In 1930 Kurzrok and Lieb[76] noted that human seminal fluid relaxed strips of smooth muscle from the uterus of women who had previously been pregnant but caused contraction of similar strips from the uterus of sterile women. This initial observation that semen contained a factor with a specific and differential function was rapidly amplified in independent reports by Goldblatt[41] and von Euler.[139] However, almost 25 years passed before prostaglandins were isolated in crystalline form,[14] their structures elucidated,[17] and the pathway for their biologic synthesis characterized.[15, 136]

Prostaglandins are 20-carbon fatty acids (molecular weight about 340) consisting of two aliphatic side chains and a cyclopentane ring. Based on differences in the cyclopentane ring, prostaglandins are divided into at least three major groups: PGE, PGA, and PGF (Fig. 18-1); within each of these groups, the prostaglandins are subdivided by the number of unsaturated double bonds in the side chains. Thus, for example, PGE_2 represents a member of the E group of prostaglandins with two double bonds in the side chains. Subtle chemical altera-

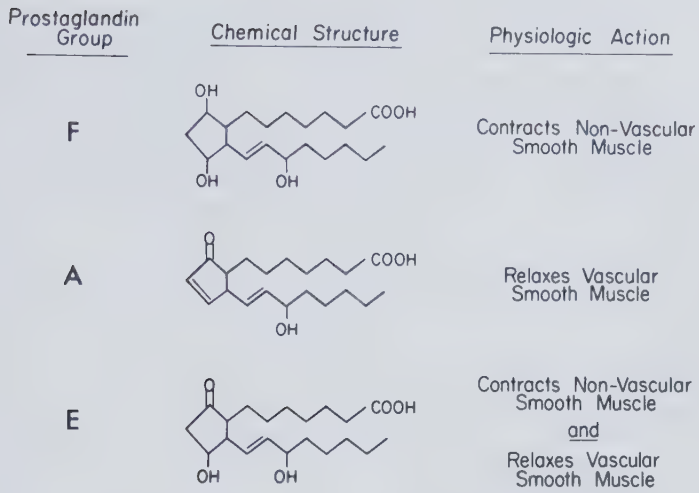

Fig. 18-1. Profile of the prostaglandins: structure and predominant action of PGE, PGA, and PGF.

tions predominantly in the ring but also to a lesser extent in the side chains are responsible for significant differences in biologic activity. Although it is a gross oversimplification, it is convenient to ascribe the predominant actions of nonvascular smooth muscle contraction to PGF, vascular smooth muscle relaxation to PGA, and nonvascular smooth muscle contraction *and* vascular smooth muscle relaxation to PGE. This simple profile, summarized in Fig. 18-1, is useful in keeping the more complex activities of the prostaglandins in perspective.

It is impossible to understand prostaglandin physiology without understanding the mechanisms by which prostaglandins are biosynthesized and metabolized. The initial step in the biosynthesis of prostaglandins appears to be the activation of tissue phospholipase A. Activated phospholipase A cleaves phospholipids, liberating straight-chain unsaturated fatty acids. By the successive incorporation of 2-carbon moieties, the chains are lengthened to 20 carbons. These 20-carbon unsaturated fatty acids are converted to prostaglandins[112] by a process of oxidative cyclization.[95, 129] As prostaglandins are essentially ubiquitous, it must be apparent that virtually all cells contain the necessary precursors and enzymes responsible for prostaglandin biosynthesis. This certainly appears to be the case. It must also be emphasized that although the biosynthetic process seems complicated, the entire sequence from the activation of phospholipase A to the ultimate release of active prostaglandins can be accomplished within seconds. Finally, it has recently been learned that the fatty acids that participate in the biosynthetic sequence are the same as those that effectively prevent the syndrome of "essential fatty acid deficiency."[101]

Prostaglandins of the E and F groups are almost totally inactivated during a single passage through the lungs[37, 98]; the enzyme 15-hydroxy prostaglandin dehydrogenase,[4, 110] present in pulmonary tissue, converts the active circulating forms to 15-keto derivatives that are largely inactive.[114] The remaining steps in the metabolic degradation can occur in plasma as well as in tissue. The 15-

keto derivatives are first reduced and then, by oxidation, shortened to 16-carbon dicarboxylic acids that are excreted in urine.[43, 112] By measuring the daily output of these "tetranor" derivatives, Samuelsson[113] has determined that humans synthesize extraordinarily small amounts of prostaglandins, in the range of 18 to 300 μg of PGE and 36 to 120 μg of PGF compounds/day. In understanding the route of inactivation, it is important to realize that the circulating half-life of PGE and PGF compounds is on the order of 1 min.[72] This short period of activity severely limits the usefulness of PGE and PGF compounds as therapeutic agents. In addition, the rapid turnover necessitates enormous increases in prostaglandin release from tissue to cause even small elevations in circulating levels of PGE and PGF.

Prostaglandins of the A group are metabolized by an entirely different mechanism. PGA compounds pass through the lungs virtually without inactivation.[84] Although the details of PGA metabolism have not been determined, the initial step in one suggested route occurs in the plasma and is affected by a plasma isomerase.[62, 99] The renal cortex and liver also seem to participate in PGA degradation. The half-life of circulating PGA is considerably longer, presumably on the order of 10 min. This is reflected by a more durable response to infused PGA compounds[63] as well as by higher plasma levels of PGA than of both PGE and PGF.[58, 149]

An important recent observation is that aspirin and indomethacin strongly inhibit prostaglandin synthesis[38, 127, 138] both in vivo[59, 112, 149] and in vitro.[27, 133] This effect explains a number of actions of the anti-inflammatory drugs. For example, the thrombocytopathy induced by aspirin is now known to be caused by failure of the secondary phase of aggregation; this particular phase of the clotting process requires the participation of PGE_2.[122] In addition, the anti-inflammatory properties of aspirin and indomethacin attest to the role of prostaglandins in the inflammatory process.[45] Numerous other examples will be discussed in subsequent sections of this chapter in conjunction with the appropriate situations. The ability to specifically suppress concentrations of prostaglandins (with aspirin and/or indomethacin) should greatly aid in evaluating the physiologic importance of the prostaglandins.

POSSIBLE ROLE IN PHYSIOLOGY

An important unanswered question is whether or not prostaglandins are hormones in the classic sense. By this definition it would be implied that prostaglandins are synthesized by one tissue and travel via the bloodstream to a second tissue where they exert their effect. If circulation via the blood is essential to the effectiveness of action of the prostaglandins, then prostaglandins should be detectable in plasma. Prostaglandins have only recently been measured in plasma, since sufficiently sensitive methods for their measurement have only been developed in the last 3 years. This point necessitates a short discussion of the methods for the measurement of prostaglandins.

Methods for estimating prostaglandins have utilized biologic, chemical, and immunologic approaches. A large number of tissues and organ systems have served in biologic assays,[16, 63, 65] but the method currently utilized with the greatest success is the superperfusion bioassay developed by Vane[137] that uses

three strips from three organs in sequence. This technique is particularly suited to the measurement of prostaglandin release by isolated organs.[29]

Among the chemical methods, absorption spectrophotometry is not nearly sensitive enough, being useful only in the microgram range.[3, 120] However, the combination of gas-liquid chromatography and mass spectroscopy can be used to measure subnanogram levels of prostaglandins[6, 44] and has an additional advantage in that it can be applied to the measurement of prostaglandin metabolites.[44]

Radioimmunoassay has also recently been applied to the measurement of prostaglandins. Immunoassay systems have been developed for prostaglandins E^{58}, A,[58, 149] and $F^{24, 72, 80}$ as well as for several metabolites.[44, 81, 82] Using radioimmunoassays sensitive to 5 pg, prostaglandins of the E, A, and F groups have been measured in normal human plasma.[24, 46, 58]

Elevated levels of prostaglandins have been documented in the peripheral plasma of patients with medullary carcinoma of the thyroid[58, 64, 143] and of women during active labor.[22, 49, 117] Both of these situations are associated with contraction of nonvascular smooth muscle and result in diarrhea and uterine contractions, respectively. Under these circumstances, it seems entirely plausible that prostaglandins function as classic hormones. However, there are at least an equally large number of situations in which prostaglandin-related actions are not associated with measurable increases in circulating levels of prostaglandins. Under these circumstances, prostaglandins do not conform to the classic definition of hormones.

Although a conclusive answer to this question is not yet available, it is now generally accepted that the role of prostaglandins is that of local modulators of cellular responses to specific stimuli. In this regard, prostaglandins are instantly synthesized on demand, act locally, and are rapidly metabolized at the same or an adjacent site.[77]

Having established that prostaglandins are basically local modulators, it becomes important to evaluate their mechanism of action. The relationship between prostaglandins and cyclic AMP assumes paramount importance in this regard. It has been generally accepted that cyclic AMP is the "second messenger" or the intracellular mediator of the response to hormonal stimuli.[21] Depending on the tissue studied, prostaglandins of the E type either increase[109] or decrease[23] concentrations of cyclic AMP. This apparent paradox emphasizes the complex nature of the relationship between prostaglandins and cyclic AMP.[52, 105, 121] Prostaglandins obviously can stimulate either adenyl cyclase (the enzyme system responsible for the synthesis of cyclic AMP) or phosphodiesterase (the enzyme that degrades cyclic AMP).[50] In situations where prostaglandins stimulate cyclic AMP concentrations, two possibilities exist: receptive cells may have sites for both prostaglandins and hormones, in which case PGE and hormones would both be "first messengers," and cyclic AMP would be the common "second messenger." Alternatively, cells activated by the presence of hormone ("first messenger") in the receptor synthesize PGE, which would in this case represent the "second messenger"; subsequent PGE stimulation of adenyl cyclase would result in synthesis of cyclic AMP, now the "third messenger."

Cyclic AMP alone cannot account for the diverse effects of the prosta-

glandins. It has recently been suggested, for example, that cyclic GMP is to PGF what cyclic AMP is to PGE.[75] The importance of cell membrane–bound ionized calcium has also recently been emphasized.[104]

SPECIFIC SURGICAL IMPLICATIONS

Oncology

Prostaglandin production by tumors of neural crest origin. Williams et al.[143] first suggested that medullary carcinoma of the thyroid (MCT) produced PGE and PGF. Using a combination of thin-layer chromatography and bioassay, four of seven tumor extracts were positive for PGE_2 and $PGF_{2\alpha}$. In addition, one of the two patients with MCT associated with diarrhea had an elevated peripheral blood level of prostaglandins, with a 10-fold gradient in the venous drainage of the tumor. These observations were expanded to include other amine-peptide–secreting tumors, including two tumors of neural crest origin (ganglioma and neuroblastoma), four pheochromocytomas, two foregut tumors (bronchial carcinoid and islet cell [α] tumors of the pancreas),[115] and seven Kaposi's sarcomas.[20] In contrast, using the same quantitative techniques, Bernier et al.[19] were unable to substantiate the prostaglandin elevations in patients with MCT.

Using a prostaglandin radioimmunoassay, we have documented elevated PGE levels in three of three patients with carcinoid tumors, two of three patients with MCT,[58, 64] and three of four patients with pheochromocytomas. The highest circulating level seen was in a 5-month-old infant with a neuroblastoma associated with severe diarrhea. In patients with these malignancies the elevated circulating levels of prostaglandins almost surely contribute to the symptomatology. For example, a number of these patients have diarrhea; the diarrhea can be reproduced by intravenous infusion of PGE_2 and $PGF_{2\alpha}$ (the two compounds synthesized by these tumors). In addition, Oates and Butler[96] have demonstrated in patients with the carcinoid syndrome that there was a poor correlation between the symptoms and the levels of serotonin; they postulated that other compounds might be involved. Since prostaglandins are synthesized in large quantities in some patients with carcinoid tumors and can mimic virtually all the effects of serotonin (including vasodilatation, diarrhea, and bronchoconstriction), they are likely candidates. Another important observation is that the tumors that produce large quantities of PGE and PGF compounds are also those that compose Sipple's syndrome.[125] Aspirin and indomethacin may be therapeutic in patients with disseminated MCT and carcinoid syndrome because of their ability to inhibit prostaglandin synthesis.

Hypercalcemia of cancer. Transplantable mouse fibrosarcoma $HSDM_1$ in vitro secretes a bone-resorbing factor into the tissue culture medium.[42] Levine et al.[83] have demonstrated that $HSDM_1$ produces large quantities of PGE_2. Based at least partly on the suggestion that prostaglandins stimulate bone resorption in vitro,[73] Tashjian et al.[130] have identified the bone-resorbing factor produced in vitro as PGE_2. Mice bearing $HSDM_1$ had pronounced hypercalcemia as well as higher serum levels of PGE_2 than normal controls. Treatment of these mice with indomethacin reversed both the hypercalcemia and the hyperprostaglandinemia.[131] A clinical corollary is obvious. A substantial number of patients with hypercalcemia associated with cancer (in the absence of bony metastases) have normal circulating levels of immunoreactive parathyroid hor-

mone.[100] It is quite possible that in at least some of these patients PGE_2 is the etiologic agent; in this case the drug of choice for the management of the hypercalcemia would be aspirin or indomethacin. This intriguing hypothesis is currently being investigated.

Prostaglandin control of cell proliferation. Prostaglandin production by tumors has been demonstrated by several investigators.[27, 83, 128] Jaffe et al.[56, 57] as well as Hammarström et al.[47] have demonstrated that neoplastic tissues in vitro produce substantially more PGE than the corresponding normal tissues. Apps and Carter[5] have suggested that prostaglandin production by tumors is strongly related to the inflammatory process.

Using a variety of pure cell lines in monolayer culture, we have correlated prostaglandin synthesis with rates of cell proliferation.[48, 60, 132] (Virtually all the prostaglandin produced was PGE; PGA and PGF accounted for less than 10% of the total.[48]) In all cell lines tested, an inverse relationship has been demonstrated; i.e., faster growing cells produced smaller amounts of prostaglandins. Increasing the concentration of PGE in tissue culture media either exogenously by adding PGE_1 or endogenously using a derivative of cyclic AMP resulted in pronounced inhibition of cell proliferation (22% to 74%). On the other hand, inhibition of PGE synthesis by including indomethacin in the medium significantly stimulated cell proliferation (18% to 23%). These data suggest that PGE may be involved in the control of cell proliferation.

The implications of these preliminary experiments appear to be significant. By manipulating concentrations of PGE in vitro and in vivo, substantial changes in rates of cell replication and tumor growth can be induced.

Shock and ischemia

Evidence has recently been presented that endotoxemia is associated with elevated circulating levels of prostaglandins. Using crude chromatographic techniques and vasodepressor bioassays, Kessler et al.[70] measured PGA release by endotoxin in dogs; with the techniques described it is impossible to be certain that the prostaglandin released was not indeed PGE. Using a sensitive radioimmunoassay, Anderson et al.[2] measured endotoxin-mediated release of PGE from the canine kidney (12-fold increase in the renal vein) and mesenteric viscera (fourfold increase in the portal vein). In addition to the stimulation of PGE release, Nakano and Prancan[93] have demonstrated that in endotoxic shock the lungs and kidneys have an impaired ability to metabolize PGE because of decreased concentrations of the inactivating enzyme prostaglandin dehydrogenase.

In 1971 Glenn et al.[40] noted that PGE_1 substantially improved both the cardiovascular hemodynamics and the rate of survival of dogs given *Escherichia coli* endotoxin. On the other hand, in subsequent reports, Nakano and various associates demonstrated that PGE_1 offered no hemodynamic or survival advantage in endotoxemic dogs[94] and perhaps was even detrimental to the treatment of endotoxic shock in mice.[92]

The observations that circulating levels of prostaglandins are high in endotoxemia and that prostaglandins may be useful in the therapy of endotoxic shock are not necessarily incompatible. This apparent paradox suggests an important aspect of the hemodynamic role of prostaglandins. PGE and PGA appear to be

important regulators of regional flow. In situations in which regional blood flow is decreased, the PGE released is protective; i.e., it increases flow to the ischemic area. Renal ischemia serves as a good example. Ischemia sufficient to cause renal hypertension results in the release of PGE into the renal veins.[34, 59, 85] PGE (and PGA) ordinarily increases renal blood flow,[61, 78] but in dogs with renoprival hypertension, infusions of PGE_1 and PGA_1 have even more pronounced effects than in normotensive dogs.[89] The situation with endotoxemia is somewhat analogous. Decreased tissue perfusion results in the release of prostaglandins, which in turn are protective and increase regional blood flow. The administration of exogenous PGE could reinforce this beneficial effect.

Machiedo et al.[86] have reported that in hemorrhagic shock PGE_1 increased both the survival and cardiac output in dogs. Hypovolemic shock is accompanied by decreased cardiac output and increased peripheral vascular resistance. PGE_1 and PGA_1 have potent cardiovascular effects; they decrease peripheral resistance and central venous pressure, increase cardiac output, heart rate, and coronary, renal, and cerebral blood flows,[88, 90] and have a direct effect on myocardial contractibility.[91] Despite their hypotensive effects, prostaglandins are potentially useful therapeutic agents in low-output states either associated with hypovolemic shock or cardiac failure or following cardiac surgery.

Platelets, coagulation, and erythropoiesis

Platelets and coagulation. In the normal scheme of coagulation, platelet aggregation triggers a complex series of events resulting in the formation of a thrombus. Platelet aggregation is therefore essential to normal homeostasis. Using turbidometric methods and following changes in absorbency, it has become clear that there are actually two phases of platelet aggregation. Stimulated in the presence of low concentrations of adenosine diphosphate, the first phase is readily reversible; the subsequent second phase is less readily reversed. Recognizing the independence of these two phases of platelet aggregation is essential to the understanding of the relationship between PGE and the process of coagulation. PGE_1 inhibits both phases of aggregation[122]; this property is currently being exploited in blood banking. In contrast, PGE_2 also inhibits the first phase of aggregation but stimulates the second and is therefore essential to normal clotting.

PGE_1 is a potent inhibitor of platelet aggregation[35, 36] in platelet-rich plasma[74] and whole blood.[51] Since PGE_1 stimulates platelet adenyl cyclase[111] and the formation of cyclic AMP (in intact[148] and disrupted[147] platelets), it appears that the inhibitory action of PGE_1 on platelet aggregation is mediated by cyclic AMP. Several laboratories have utilized this dispersive property in the preparation of platelet-rich plasma and platelet concentrates.[9, 123, 134] Summarizing the effectiveness of these trials it is clear that the addition to blood of PGE_1 (> 10 ng/ml) (1) substantially improves the recovery of viable platelets, (2) prevents the microaggregation of platelets while maintaining normal platelet shape in vitro, (3) does not alter the survival time of transfused platelets in vivo, and (4) does not decrease the effectiveness of transfused platelets on the restoration and maintenance of normal homeostasis. The advantages are obvious; platelet harvesting and storage can be improved without altering the effectiveness of the retransfused platelets. The concentration of PGE_1 required to maintain these

effects is low, and because of the combination of dilution and rapid inactivation, the PGE_1 administered with transfusion produces no untoward side effects. Another advantage is in the production of platelet-free red cell preparations useful as blood transfusions for patients awaiting renal transplants. The addition of prostaglandins to whole blood does not alter the affinity of red cell hemoglobin for oxygen.[28]

In contrast to PGE_1, PGE_2 appears to be essential to normal platelet function. In the presence of thrombin, platelets produce PGE_2,[124, 126] which mediates the second phase of aggregation. PGE_2 restores normal platelet function to platelet-rich plasma in patients with von Willebrand's disease.[135] The importance of PGE_2 in coagulation is further emphasized by the recent discovery that aspirin and aspirin-like drugs inhibit prostaglandin synthesis.[38, 127, 138] The deficiency of PGE_2 almost undoubtedly explains the etiology of aspirin-induced thrombocytopathy. A final interesting observation is that low concentrations of PGE_2 (10 ng/ml) can induce sickling of red cells from susceptible patients, i.e., those with S hemoglobins; no such effect was noted in patients with normal erythrocytes.[144] It is thus possible that increased levels of PGE_2 may precipitate sickle cell crisis.

Erythropoiesis. An additional effect of the prostaglandins appears to operate in erythropoiesis. Prostaglandins potentiate the effects of the renal hormone erythropoietin[142] and stimulate erythropoiesis in polycythemic mice.[118] Dukes et al.[32] have rated the effectiveness of the erythropoietic action as $PGA_2 > PGE_2 = PGA_1 > PGE_1$. The mechanism of this action is uncertain. Two possibilities have been proposed: (1) that the effect is mediated by the redistribution of renal blood flow[118] and (2) that it is a direct effect or red cell generation.[30, 31]

Gastrointestinal function

Gastrointestinal prostaglandin content and release. The gastrointestinal tract is a rich source of prostaglandins. PGE_1, PGE_2, PGA_1, $PGF_{1\alpha}$, and $PGF_{2\alpha}$ have each been isolated from some portion of the tract. The distribution of prostaglandins varies among different species and among different organs studied. As a general rule, the human stomach and intestines contain mainly PGE_2, whereas those of animals contain PGE_1, PGE_2, and $PGF_{2\alpha}$.[12, 13, 146] Although prostaglandins have been detected in animal liver, they have not been documented in the human liver.[67, 68]

Although prostaglandins can be measured in all portions of the gastrointestinal tract, and they are undoubtedly released spontaneously, a number of stimuli have been identified that increase the rate of prostaglandin release from the gastrointestinal tract. These stimuli include gastrin,[119] pentagastrin,[103] histamine,[103] cyclic AMP,[119] acetylcholine,[8] and vagal stimulation.[26, 102, 146] The exact "physiologic" role played by prostaglandins in the gastrointestinal tract is unknown, but their presence and stimulated release imply that they may have a regulatory role. The areas that have been most carefully studied include intestinal motility and absorption and gastric acid secretion.

Intestinal motility and absorption. PGE and PGF compounds have differential actions on intestinal smooth muscle. In general both groups of prostaglandins contract intestinal longitudinal smooth muscle,[53, 140] but the circular smooth muscle is relaxed by PGE compounds[11] and contracted by PGF deriva-

tives.[39] Intravenous infusion of PGE_2 and $PGF_{2\alpha}$ understandably results in severe abdominal cramps.[18, 66] In addition, the prostaglandins inhibit absorption of electrolytes and water from the small bowel.[1, 87] As in patients with MCT (see foregoing discussion), the overall effect of infusion or elevated circulating levels of PGE_2 and $PGF_{2\alpha}$ is colicky abdominal pain and profound diarrhea. The effects of prostaglandins on small bowel function mimic the effects of cholera enterotoxin.[71] It has been demonstrated that the diarrhea observed in clinical cholera is associated with the accumulation of cyclic AMP in the small intestinal mucosa.[97, 116] Since prostaglandins stimulate cyclic AMP formation in a variety of tissues, and specifically in the small bowel mucosa,[116] it has been suggested that prostaglandins may be involved in the mediation of the effects of cholera enterotoxin on the small intestinal mucosa.[10] If that were true, the use of aspirin and/or indomethacin might attenuate these effects.[10] In the study by Jacoby and Marshall,[55] aspirin and indomethacin did inhibit the cholera enterotoxin–mediated increase in intestinal fluid in ileal-ligated rats. The mere possibility that anti-inflammatory compounds may modify the course of clinical cholera (by inhibiting prostaglandin synthesis) is exciting and warrants further investigation.

Gastric acid secretion. There have been numerous studies that document that prostaglandins inhibit basal and stimulated gastric acid secretion in humans[25] as well as in animals.[7, 107, 108] The mechanism of this action is not entirely clear. Since only PGA and PGE compounds are effective, it is interesting to speculate that alterations in mucosal blood flow may be responsible. The studies of Wilson and Levine[145] as well as those of Jacobson[54] have convincingly demonstrated an inhibitory effect on the secretory mucosa that causes the observed decrease in mucosal flow. Moreover, prostaglandins are effective inhibitors of acid secretion in vitro.[141] Attempts to implicate cyclic AMP in the mechanism have resulted in contradictory data and no satisfactory explanation.

Intravenous infusions of PGA and PGE compounds in doses large enough to suppress rates of gastric acid secretion also result in a number of undesirable side effects, including hypotension, intestinal colic, and nausea. Administered orally, natural prostaglandins are largely ineffective. A recent chemical discovery, however, has increased the likelihood of using prostaglandins therapeutically to decrease acid secretion; three orally effective prostaglandins have been synthesized. These compounds, 15(R)-methyl prostaglandin E_2, 15(S)-methyl prostaglandin E_2, and 16,16-dimethyl prostaglandin E_2, are blocked (chemically or sterically) at the position at which natural PGE_2 is vulnerable to inactivation by oxidation. They thus have much longer effective half-lives, are absorbed from the gastrointestinal tract, and are effective at considerably lower doses, obviating some of the problems with side effects. In two studies these drugs have successfully inhibited gastric acid secretion in dogs[106] and humans.[69] It thus appears that, as suggested in an editorial in the *Journal of the American Medical Association* in 1969,[33] prostaglandins and/or prostaglandin derivatives may be useful in the management of peptic ulcer disease. Lee et al.[79] have already shown that PGE_2 decreases ulcer formation in an experimental rat model for peptic ulceration. Extension of these observation and application to humans could be a breakthrough in the prophylaxis and treatment of peptic ulcer disease.

SUMMARY AND CONCLUSIONS

The complete range of actions of the prostaglandins and their potential applications to clinical surgery cannot possibly be described in a single chapter of limited length. In addition to the several areas described here, prostaglandins have been implicated in the regulation of pressure in the anterior chamber of the eye, renal excretion of water and electrolytes, uterine and ovarian function, pulmonary vascular hemodynamics and airway mechanics, mediation of inflammation, and transmission of nervous impulses.

Clinical and experimental studies with prostaglandins are increasing exponentially. If progress continues at the present rate, within a fairly short period of time many of the questions already posed should be answered, and prostaglandins and/or prostaglandin analogs will probably be firmly entrenched in the pharmacologic armamentarium.

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19

Interposition mesocaval shunt

THEODORE DRAPANAS

The diversion of portal blood into the systemic circulation as a method of decompression of the portal system in patients with portal hypertension has been utilized for the past 30 years. Nevertheless, although there is unquestionable protection against variceal hemorrhage by such procedures, many problems continue to plague the surgeon. Primary among these is the high surgical mortality in the poor-risk patients who are offered such procedures. This mortality ranges from 15% to 30% in poor-risk patients when the usual shunts, e.g., end-to-side and side-to-side portacaval, splenorenal, or distal splenorenal, are applied. Additionally, the use of "makeshift" shunts is also attended with a high incidence of thrombosis, rebleeding, or inadequate decompression. The problem of postoperative ascites is also not uncommonly seen, particularly after an end-to-side portacaval shunt that does not adequately decompress the hepatic parenchyma.

Finally, a high incidence of hepatic encephalopathy has been reported following surgical procedures that totally divert portal blood flow from the liver. Because of these and other problems a number of surgeons have recently questioned the value of standard shunting techniques in the management of portal hypertension. Indeed a number of recent reports have failed to confirm any increased survival in controlled series of patients after portacaval shunts for variceal hemorrhage as compared to patients not undergoing the shunt procedure. Although the former group is well protected against recurrent hemorrhage, there is a higher incidence of hepatic failure than in those patients who are not offered shunts, and at the end of 5 years there is no significant difference in surviving patients between the two groups.[12]

Based on previous experiences with portosystemic shunts[8] and on recent reports evaluating a significant number of patients,* the fact that many of the

*See references 1, 6, 7, 18, 25, and 32.

poor-risk patients died as a result of liver failure or other complications in the immediate postoperative period made a marked impression as early as several years ago. However, once the patient recovered from the operative procedure and was discharged from the hospital, his chances of survival were not too dissimilar from those of the better-risk patient with good hepatic functional reserve. It became apparent that if the surgical procedure could be simplified, thereby offering less surgical trauma and the avoidance of multiple blood transfusions during the operative procedure in the critically ill patients, improvement in surgical mortality would result. Additionally, it was believed that the type of shunt utilized should both offer the possibility of decompression of the hepatic parenchyma in those patients with high intrahepatic sinusoidal pressure and severe ascites and at the same time permit the perfusion of the hepatic sinusoid in those patients who had high prograde portal blood flow to the liver after the shunt.

In 1969 prospective evaluations were begun of a large-diameter Dacron graft interposed between the superior mesenteric vein and the inferior vena cava (interposition mesocaval shunt) for the management of variceal hemorrhage resulting from cirrhosis of the liver and portal hypertension.[9] Such efforts to bridge the gap between the portal system and the systemic venous system had previously been made by Reynolds and Southwick,[29] Theron,[31] Erlik et al.,[10] Batancourt et al.,[2] Dale and Scott,[7] Nay and Fitzpatrick,[23] Nabseth et al.,[22] Lord,[17] Lord et al.,[15] Yeoh and Eiseman,[36] Foster et al.,[11] Symbas et al.,[30] Preston and Trippel,[26] and Read et al.[27] These preliminary studies indicated that venous grafts or synthetic grafts interposed between the portal system and the vena cava did indeed remain patent, presumably as a result of the differential in pressure between these two venous systems. Furthermore, in the scattered instances when these procedures had been utilized for portal hypertension in patients, adequate decompression of the portal circulation resulted.

Among the first to report on the technique of interposition mesocaval shunt were Lord et al.[16] who in 1970 inserted a woven Teflon graft in three patients and demonstrated continued patency. In the same year, Read et al.[27] utilized venous homografts (jugular vein) and also demonstrated excellent graft patency rates.

The purpose of this chapter is to review the technique of interposition mesocaval shunt that has been utilized during the past 6 years and to present the methods of patient selection, the pre- and postoperative care, the results of hemodynamic studies, and the long-term survival in a series of 80 patients who have been offered this procedure during this period.

PATIENT SELECTION

Among the commonly used criteria for classifying patients according to operative risk for shunt procedures are those of Child[6] wherein patients are divided into groups A (excellent risk), B (moderate risk), and C (poor risk) (Table 19-1). Although this procedure was initially performed only in moderate- or poor-risk patients, the results to date have been so promising that these standards have now been extended to make the operation available to even the excellent-risk (A) group. Of the 80 patients in whom this operation has

Table 19-1. Disease classification of patients with hepatic cirrhosis

	Group A (minimal)	Group B (moderate)	Group C (advanced)
Serum bilirubin (mg%)	Below 2.0	2.0-3.0	Over 3.0
Serum albumin (Gm%)	Over 3.5	3.0-3.5	Under 3.0
Prothrombin time (sec)	11-15	15-20	Above 20
Ascites	None	Minimal	Intractable
Encephalopathy	None	Mild	Coma
Nutrition	Excellent	Good	Poor, wasting

Table 19-2. Groupings of patients undergoing operation for interposition mesocaval shunt

Groups	No. of patients
A (excellent risk)	7
B (moderate risk)	36
C (poor risk)	37
Total	80

been performed to date, there were 7 patients in group A, 36 patients in group B, and 37 patients in group C (Table 19-2). Therefore the majority of these patients were not excellent operative risks. Six patients had postnecrotic cirrhosis and 74 patients had nutritional cirrhosis of Laënnec's type. This distribution of patients to within the moderate- and poor-risk categories is not unusual considering the type of patients encountered in a large eleemosynary institution such as Charity Hospital.

All of these patients had had at least one massive hemorrhage necessitating multiple blood transfusions. Indeed, fully two thirds of the patients had had more than one episode of massive upper gastrointestinal hemorrhage and at least two admissions to the hospital for hemorrhage. There were 52 men and 28 women with a median age of 46 years. The youngest patient was 21 years of age and the oldest was 69 years of age. All patients were admitted to the hospital because of acute exsanguinating variceal hemorrhage, and no prophylactic shunts were performed in any patient who had never bled despite the presence of varices. In the majority of patients the acute hemorrhage was adequately controlled by insertion of a Blakemore-Sengstaaken tube, which also permitted adequate preparation for the shunt procedure during the ensuing few weeks or months. However, in 14 of these patients the shunt was performed as an emergency or semiemergency procedure early in the patient's hospital course because of continuing or recurrent hemorrhage despite the use of esophageal balloon tamponade.

PREOPERATIVE EVALUATION

When feasible, preoperative evaluation consisted of a complete liver biochemical profile, an upper gastrointestinal series with a barium swallow x-ray

examination, and esophagogastroscopy. The latter was performed not only to confirm the presence of esophageal varices but also to eliminate other causes of massive upper gastrointestinal hemorrhage such as duodenal ulcer or alcoholic gastritis. Similarly, a complete hematologic workup, a plasma and urinary electrolyte analysis, and additional studies were obtained on most patients. A liver biopsy was also performed to confirm the diagnosis of hepatic cirrhosis if any question arose.

Over one half of the patients in the entire series presented with ascites of varying degrees at some time during the course of their disease. This was undoubtedly a result of the advanced degree of cirrhosis and the degree of hepatic sinusoidal obstruction. A common manifestation in these patients was that of secondary hyperaldosteronism manifested by an alkalotic serum, hypokalemia, increased potassium excretion in the urine, and a paradoxic aciduria. These changes were undoubtedly caused by the inability of the diseased liver to conjugate aldosterone, a finding that has been confirmed by numerous investigators.

When present, secondary aldosteronism was treated with varying courses of spironolactone with a diuretic (Aldactazide) along with sufficient potassium supplementation to restore the serum potassium and urinary pH to normal levels. Additionally, albumin in varying amounts from 50 to 500 Gm was administered, the dose depending on the level of the serum albumin at admission and on the patient's response to preoperative preparation.

Finally, in view of the hyperdynamic state commonly noted in many of these patients, cardiac reserve was carefully evaluated, including the monitoring of central venous pressure where indicated. In three patients who exhibited cardiac failure of the high-output type, digitalization was performed during the preoperative preparation.

ANGIOGRAPHIC EVALUATION

Except for the acute bleeder in whom the shunt is being done as an emergency life-saving procedure, it has been customary to perform selected celiac and superior mesenteric arteriography via the retrograde Seldinger technique and to observe the venous phase filling of the splenic, portal, superior mesenteric veins and collaterals within the abdomen. These studies have been extremely helpful in outlining the extent of collateral formation and also the suitability of the superior mesenteric vein for subsequent shunt. Equally as important was the observation that in the majority of these patients, there was a higher resting pressure in the inferior vena cava below the level of the renal veins than is usually suspected. The reasons for the latter were not readily apparent, but a number of factors are probably responsible, including the presence of ascites, the increased collateral flow to the vena cava resulting from portal hypertension and natural portosystemic shunts, the increased blood volume, and the hyperdynamic cardiovascular state. However, in one patient significant obstruction of the intrahepatic portion of the inferior vena cava caused by an enlarged caudate lobe was encountered. In one additional patient, excluded from the study, there was evidence of Chiari's syndrome, and a large thrombus was present at the orifice of the hepatic veins. This patient was treated nonoperatively with anticoagulants and there was no further evidence of hemorrhage and the ascites subsided. The progress of this patient is being carefully followed

to determine whether or not fibrosis with portal hypertension will eventually develop.

The technique of retrograde catheterization of the hepatic veins as popularized by Warren et al.[34, 35] has also been found to be helpful. This permits the measurements of hepatic vein wedge pressure and gives an accurate reflection of the sinusoidal pressure within the hepatic parenchyma. This appears to give an even more reliable index of sinusoidal pressures than does the measurement of splenic pulp pressure obtained by percutaneous splenic punctures. Such studies have provided important information concerning the intrahepatic hemodynamics. For example, retrograde filling of the portal vein has been encountered after injection of a bolus of dye into the wedged hepatic vein, indicating a reversal of portal flow in these patients. In my opinion, this obstruction indicates that not only is venous decompression of the portal vein necessary but also of the hepatic parenchyma in order to decompress the hepatic sinusoid, as previously pointed out by McDermott,[19] who has popularized the side-to-side

Fig. 19-1. Venogram showing wedged hepatic vein. Patient had advanced cirrhosis and severe ascites with high intrahepatic sinusoidal pressure (450 mm H_2O) and evidence of retrograde flow from hepatic veins into portal radicals. At surgery, flow measurements indicated reversed or stagnant flow in portal system. An end-to-side portacaval shunt, in my opinion, would have been contraindicated. An interposition mesocaval shunt was performed, and patient has done well with no further evidence of variceal hemorrhage, ascites, or encephalopathy.

or "double-barreled" portacaval shunt. An example of the type of information that can be obtained by such studies is shown in Fig. 19-1.

Warren et al.,[35] McDermott,[18] Mikkelsen,[20] and other investigators have believed it to be most important to determine preoperatively the magnitude of portal perfusion of the liver in patients eligible for shunt procedures, and they have suggested that patients with a high sinusoidal perfusion are more apt to suffer from the ravages of encephalopathy and hepatic failure if complete portal diversion is performed. Additionally, Warren has indicated that those patients with ascites and those with high intrahepatic pressures and reversed or stagnant portal flow to the liver are not suitable candidates for the selective type of distal splenorenal shunt that he has recently advocated as a means of preserving hepatic portal perfusion.

Recently, an expanded hemodynamic evaluation in these patients has been employed in an effort to better outline the pressure-flow phenomena and the sinusoidal resistance. Such studies permit the determination of an electrical analog of the portal system and give very meaningful data. However, these studies are beyond the scope of this review and will be presented elsewhere.

OPERATIVE TECHNIQUE (Figs. 19-2 to 19-7)

Exploration through a long midline incision has proved most satisfactory in my experience. Furthermore, in the presence of extensive venous collateral in the abdominal wall the midline approach appears to be less involved with vascular structures and more rapidly performed. The abdominal viscera are carefully evaluated, with particular emphasis on eliminating other possible causes for hemorrhage, e.g., duodenal ulcer, gastric ulcer, and Mallory-Weiss syndrome. At this point the liver is carefully evaluated and the degree and extent of involvement of the liver with cirrhosis is carefully noted. Particular attention is paid to the possibility of coexisting hepatoma, which has been reported to be present in from 5% to 10% of patients with long-standing cirrhosis.

Measurement of portal pressure is then performed by threading a thin wall no. 18 needle or a fine polyethylene catheter into the portal vein through a mesenteric branch. My preference is to utilize a primary division of the middle colic vein or the vein itself, a short segment of which is dissected free, encircled with a suture, and directly punctured with the needle. Mean portal pressures are obtained directly through a needle or through the catheter threaded through the needle. Alternatively, the main superior mesenteric vein may be cannulated after it is dissected free. Zero reference of the venous manometer is adjusted to the level of the right atrium and mean portal pressure is recorded.

Along with portal pressure, pressure is also measured at the inferior vena cava below the level of the renal veins at the site where the shunt will be inserted. This is believed to be an important measurement because it is the outflow pressure that determines the residual pressure in the portal vein, assuming there is no significant resistance, kinking, or obstruction of the shunt after the anastomosis. Should any question arise as to the patency of any of the portal branches or of the inferior vena cava, operative venous angiography can also be performed at this point to satisfy the surgeon that the vessels are of adequate size.

The transverse mesocolon is now elevated superiorly, and the peritoneum

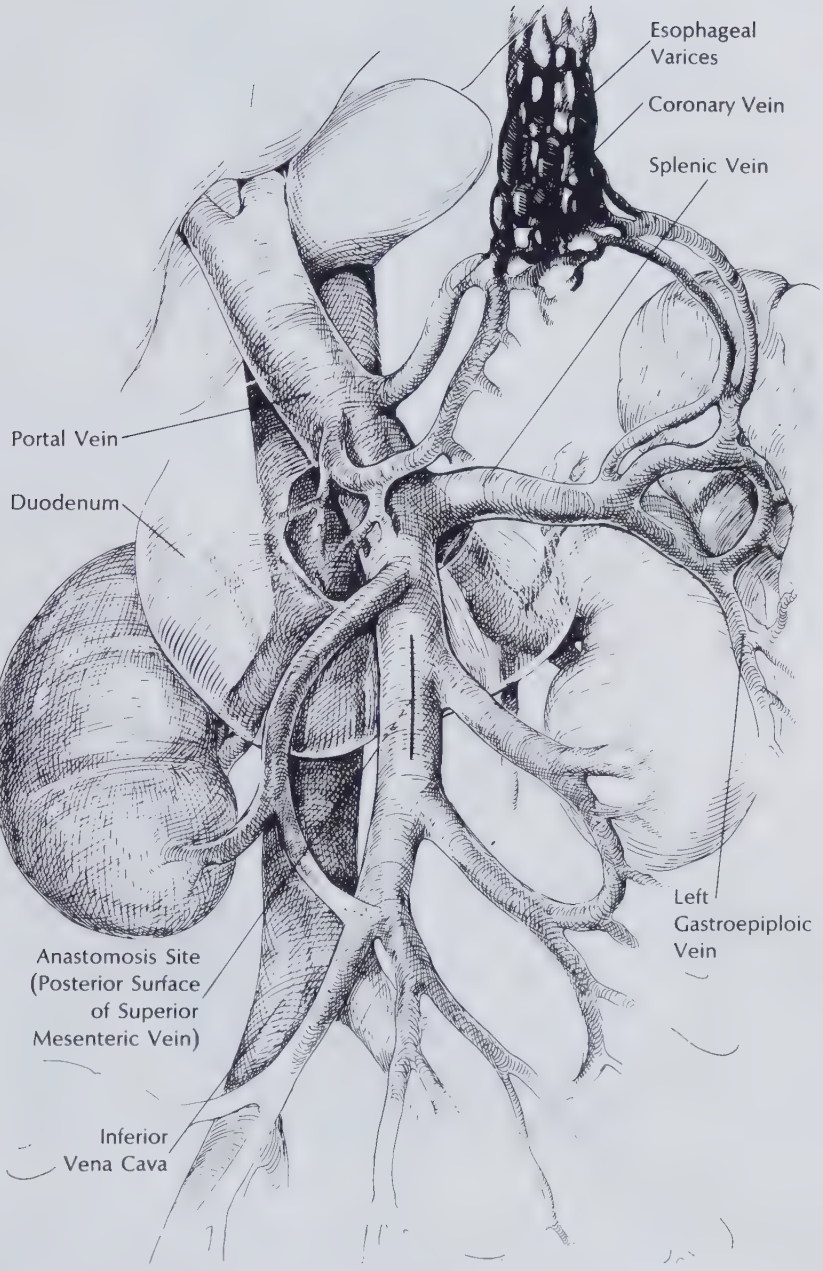

Fig. 19-2. Anatomy of portal system. Site of mesocaval shunt anastomosis is shown. This is usually located just distal to middle colic vein and proximal to major intestinal branches. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

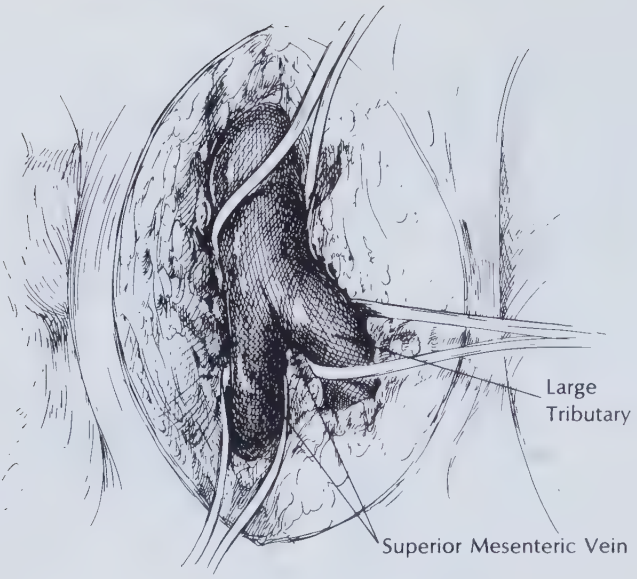

Fig. 19-3. Completed dissection of superior mesenteric vein. Large anomalous intestinal tributary is shown; it is preferable to preserve this branch. Approximately 3 cm of mesenteric vein must be dissected free to accommodate anastomosis of large Dacron graft. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

Fig. 19-4. Completed dissection of inferior vena cava. Third and fourth portions of duodenum are mobilized, and retroperitoneal space is entered through mesocolon. It is preferable not to mobilize right colon because it is unnecessary and excess bleeding may result due to the presence of large tributaries in this area. Approximately 5 cm of anterior surface of inferior vena cava is dissected free. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

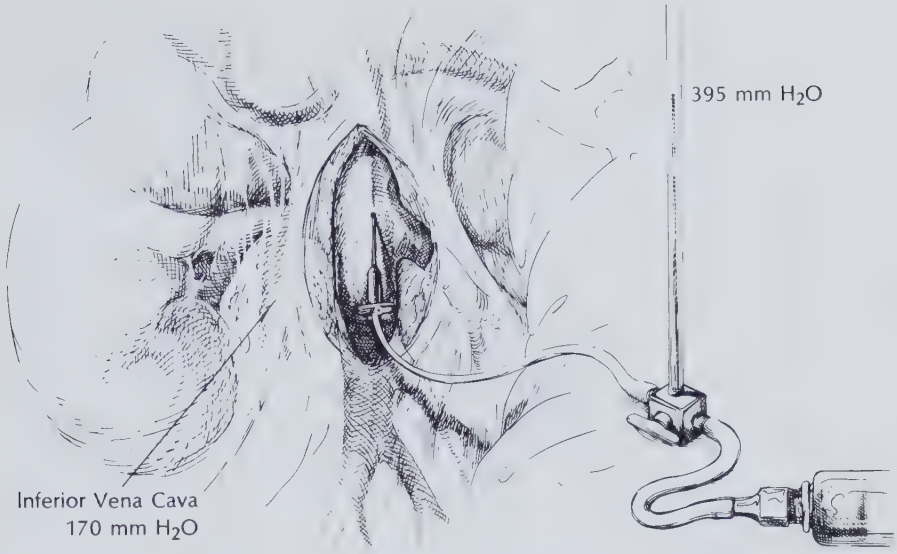

Fig. 19-5. Pressure measurements are obtained in superior mesenteric vein and inferior vena cava at site of anastomosis. Relative pressure measurements obtained from one patient are shown. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

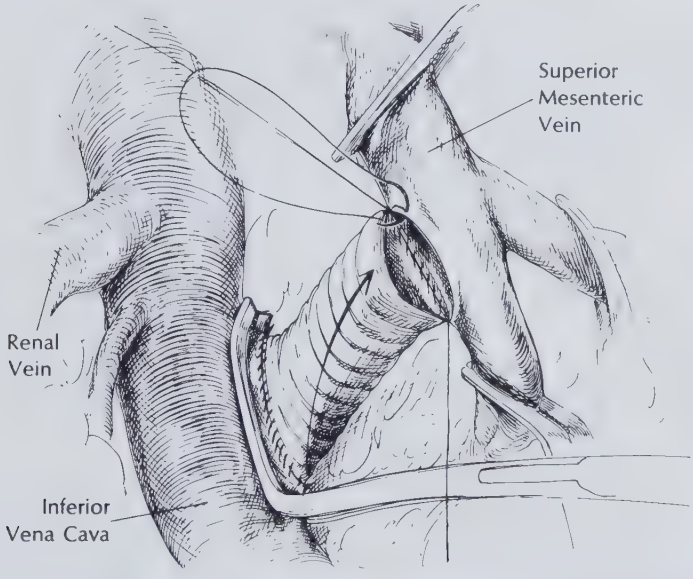

Fig. 19-6. Completed anastomosis of graft to anterior surface of inferior vena cava is shown. Graft is then trimmed and a 30-degree clockwise twist is imparted to it, followed by anastomosis of end of graft to side of superior mesenteric vein. Simple over-and-over suture is used. Posterior wall of mesenteric venous anastomosis is made from within lumen. Partially occluding clamp is on inferior vena cava but superior mesenteric vein is completely occluded with small vascular clamp, a procedure presenting no difficulty in performance. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

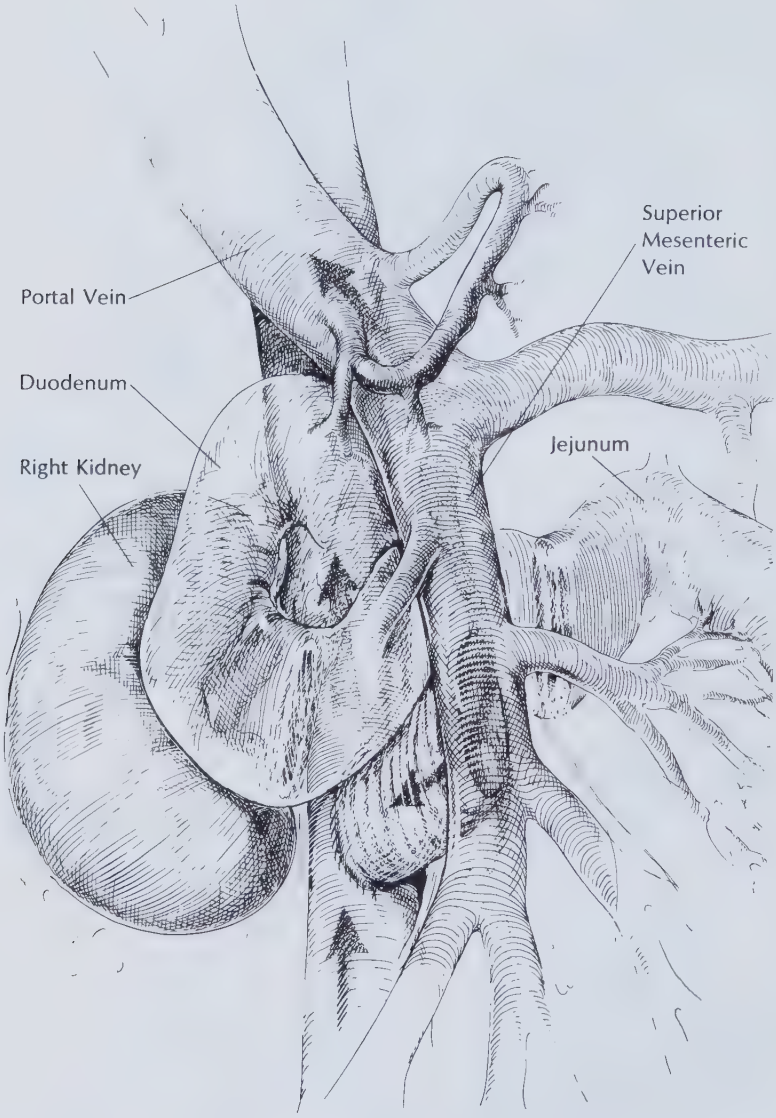

Fig. 19-7. Completed anastomosis and graft. (From Drapanas, T., and Akdamar, K.: Hosp. Pract., Sept., 1974, pp. 82-88.)

overlying the superior mesenteric vessels as they enter the root of the small bowel mesentery is opened transversely. The superior mesenteric vein is carefully freed by sharp and blunt dissection. The use of the electrocautery is preferred at this point to coagulate small but troublesome venous collaterals as well as lymphatic channels in order to prevent postoperative ascites. In approximately two thirds of the patients an adequate length (3 cm) of the superior mesenteric vein can be dissected free distal to the middle colic vein, which acts as a reference point without interruption of any major distal intestinal branches.

In the remaining third of patients, anomalies of the superior mesenteric vein are present, the most frequent of which is an early bifurcation of the superior mesenteric vein, each branch containing a significant portion of the intestinal venous flow. This branch usually lies posteriorly (when viewed from the surgeon's position at the right side of the operating table), and care must be taken to avoid injury. Rather than ligate a major branch in order to obtain adequate length for anastomosis, the preferable procedure involves careful preservation of all major branches and creation of the anastomosis of the graft directly at the point of major bifurcation of the superior mesenteric vein after temporary occlusion of each major branch with small atraumatic vascular clamps.

After complete dissection of the superior mesenteric vein, the vena cava is exposed directly through the base of the right transverse mesocolon. It is not preferable to mobilize the right colon as has been recommended by some investigators because this is frequently accompanied by troublesome bleeding resulting from interruption of large venous collaterals crossing in the retroperitoneal space and the lateral peritoneal gutter. The opening of the mesocolon permits direct visualization of the anterior surface of the inferior vena cava, which is dissected free for a distance of approximately 4 cm on its anterior, lateral, and medial portions. It is not necessary to ligate any of the lumbar collaterals, but occasionally small parietal venous collaterals must be interrupted to ensure adequate length and mobility of the inferior vena cava.

Frequently lymph node enlargement is present in the mesentery just lateral to the superior mesenteric vein. These nodes are removed to permit as straight a graft as possible to the posterolateral wall of the superior mesenteric vein and to avoid graft angulation.

Among the most important portions of the dissection is the mobilization of the duodenum as it crosses beneath the superior mesenteric vessels. In order to avoid any possible compression of the duodenum by the graft or impingement on the graft lumen by the duodenum, the third and fourth portions of the duodenum are routinely mobilized to include the ligament of Treitz. This permits the duodenum to ride up and avoids the problem of the duodenum remaining constantly present in the operating field.

The caval anastomosis is performed first because it lies in the depths of the field and the exposure is not quite as good as that of the superior mesenteric vein. A partially occluding atraumatic vascular clamp is placed on the anterior surface of the vena cava, and a small button of caval wall is removed. The anastomosis is completed utilizing a single simple running 5-0 synthetic vascular suture. On completion of the right or lateral half of the anastomosis, the clamp is pulled to the patient's right and the medial wall of anastomosis is completed with a similar suture. The anastomosis is then checked for leaks, and the graft is preclotted by permitting a column of blood to enter it while momentarily releasing the vascular clamp. I do not believe that heparinization of the patient or of the involved vessels is necessary in such patients. Furthermore, many of these patients have altered clotting mechanisms and it is my distinct impression that heparinization may even be hazardous.

After the surgeon has ascertained that the caval anastomosis is patent with no leaks, attention is then directed to the superior mesenteric vein. The graft is trimmed to adequate length, usually between 4 and 7 cm, avoiding both

tension and too long a graft, which might kink after the viscera are replaced into the abdomen.

Another important maneuver that has been found useful is that of imparting a 20- to 30-degree *clockwise* twist of the graft prior to the start of the anastomosis to the superior mesenteric vein. This is necessitated by the normal course of the superior mesenteric vein over the vena cava, which is approximately a 20- to 30-degree *counterclockwise* angle when the viscera are restored to normal position. A longitudinal venotomy is made in the superior mesenteric vein after proximal and distal occlusion with small, angled vascular clamps. I believe the superior mesenteric vein and its branches can be safely occluded during the period of anastomosis and the use of a partial occlusion clamp avoided. The anastomosis is begun on the posterior surface of the vein, which of necessity is within the lumen of the graft. After the posterior wall suture is placed, another suture is then continued anteriorly, completing the lateral wall of the anastomosis. The caval clamp is now released, and the graft should balloon out quickly. The superior mesenteric anastomosis is checked, and the small clamps on the superior mesenteric vein are also removed. Flow of more saturated superior mesenteric venous blood can be readily seen entering the vena cava through the lower anastomosis, and a decompression of the superior mesenteric vein should be readily detected when palpated with the finger.

The surgeon might be tempted in patients with a low-lying duodenum to

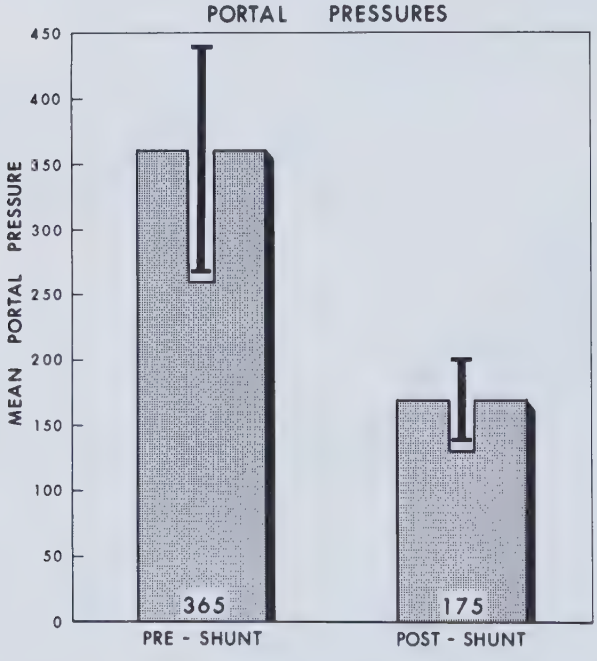

Fig. 19-8. Portal pressure. Measurements were obtained in a series of 80 patients before and after shunt. From a mean preoperative pressure of 365 mm H_2O, there was approximately a 50% drop following the shunt—to 75 mm H_2O. Standard error for mean is shown for entire group.

tunnel the graft between the duodenum and pancreas, as has been reported by other investigators. This has not only been found to be unnecessary, but is also believed extremely hazardous because of the risk of pancreatitis and troublesome hemorrhage. Pressure measurements are now obtained again from the superior mesenteric vein and the inferior vena cava at the level of the anastomosis. Because as large a graft as possible is utilized to avoid any resistance through it, little or no pressure drop should occur across the shunt. In my experience this rarely exceeds 2 cm of water. The average graft used is an 18 mm diameter knitted Dacron graft. Recently, the Weaveknit type of prosthesis has been utilized because it is softer and more readily sutured, the vascular needle more readily penetrating this material. The use of the more rigid Teflon prosthesis has not been found to be necessary and I believe further that the Dacron is more readily incorporated into the tissues than the less reactive Teflon, based on an extensive experience with these materials in peripheral reconstruction.

Other investigators, particularly Read et al.,[27] have strongly recommended the use of autogenous (jugular) vein or, alternatively, the use of a venous homograft. In my experience the use of the jugular vein as an autograft adds considerable operating time to the procedure and is totally unnecessary because equal patency has been achieved with the use of the synthetic graft in the portal system.

The pressure in the superior mesenteric or portal vein after release of the clamps and decompression should drop to approximately 40% to 60% of the preshunt pressures (Fig. 19-8). At this point it is important to emphasize that the residual pressure in the superior mesenteric vein after this type of shunt is considerably *higher* than the residual pressure usually obtained by the surgeon who is accustomed to performing a standard end-to-side portacaval shunt. This is largely a result of the higher vena caval pressure at this level of the anastomosis.

After the surgeon is satisfied that the anastomosis is technically adequate and that sufficient decompression of the portal system has occurred, the viscera are replaced and the abdomen is closed in the usual fashion. I prefer to utilize a single-layer closure of the linea alba with a heavy (no. 1) synthetic monofilament suture placed in a near-and-far or figure-of-eight technique. It does not appear necessary to close the peritoneum as a separate layer. If the patient is particularly obese, the subcutaneous space is also closed with interrupted sutures, followed by closure of the skin with a fine synthetic suture. No drains are utilized. The entire operative procedure occupies from 1 to 3 hr with an average of 1½ hr operating time, depending on the degree of collateral formation, obesity, and whether or not anomalies are present to complicate the dissection of the superior mesenteric vein. In my experience this is less operative time than required for some of the more complicated selective shunts or even for the usual portacaval shunt.

POSTOPERATIVE CARE

Care must be taken during the postoperative period to avoid protein depletion because a number of patients will experience some accumulation of ascites caused by interruption of the large lymphatic channels during the dissection, even though every effort is made during the operative dissection to

coagulate these lymphatics as they are encountered. For this reason and also because many of these patients have a low serum protein level preoperatively, 50 Gm of salt-poor albumin is infused every 12 hr during the first 48 hr after surgery.

The serum electrolytes are carefully monitored postoperatively, paying particular attention to the potassium level and to the arterial pH of the blood. Many patients, despite preoperative treatment with spironolactone, develop hypokalemic alkalosis. This metabolic derangement should be avoided because encephalopathy may be precipitated. In the usual patient, 80 to 120 mEq of potassium is administered daily for the first 3 or 4 postoperative days, depending on the serum potassium levels and renal function.

By the third postoperative day, most patients will have exhibited a brisk diuresis. By this time they have already started oral alimentation and are ambulatory. The diet is rapidly progressed to a full house diet; the avoidance of protein recommended by some investigators has not been found to be necessary. Also, no high incidence of postoperative encephalopathy has been encountered in these patients, a finding reported by other researchers to occur following the completely diverting, end-to-side portacaval shunts.

Should ascites of any significant amount occur in the immediate postoperative period, the sodium intake is limited to less than 100 mEq/day, fluids are restricted to less than 1 L/day, and occasionally a diuretic such as furosemide (Lasix, 40 ml/day) is used. When diuretics are utilized, supplemental potassium *must* be administered in order to avoid hypokalemia and alkalosis.

The patient can usually be discharged 7 to 10 days postoperatively, depending on his course and response to surgery. Of interest has been the further observation that those patients in whom hypersplenism has existed preoperatively have occasionally exhibited a prompt response with remission of the hypersplenism. However, in the majority of patients hypersplenism may be prolonged for 6 months to 1 year, and there is no need to perform splenectomy either simultaneously with the performance of the shunt or in the immediate postoperative period. Splenectomy was performed because of continued hypersplenism in only one patient in the entire series to date.

If a patient exhibits secondary hyperaldosteronism preoperatively, I also prefer to continue spironolactone administration for at least 6 months postoperatively and to follow the electrolyte status extremely carefully. Also, liver function tests are performed on one to two occasions during the immediate postoperative period and at frequent intervals following discharge in order to monitor the progress of the liver disease in these patients.

PATENCY OF GRAFTS

Follow-up studies of graft patency have been performed in 45 of these patients at varying intervals after the shunt procedure. In these patients all of the grafts except two have remained patent. In one of the patients with an occluded graft who subsequently underwent reexploration, it was discovered that the surgeon who performed the procedure utilized too small a graft (8 mm). Predictably occlusion of the graft resulted from excessive resistance to venous blood flow and possibly turbulence through such a small shunt. This patient was readmitted with hemorrhage and an effort was made to insert a larger graft.

However, the patient's liver function was not sufficiently good to survive the operation and repeated hemorrhage, and he died of liver failure.

The second patient, in whom an occluded graft was found, was readmitted 6 months postoperatively with recurrent variceal hemorrhage. After control of the hemorrhage with a Blakemore-Sengstaaken tube, reexploration revealed kinking of the graft, possibly caused by excess length. Because of technical difficulties a new graft could not be inserted in the same location and a standard end-to-side portacaval shunt was performed. The patient had an unremarkable postoperative course and continues to do well 8 months after his second pro-

Fig. 199. Retrograde cannulation of shunt demonstrating patency of graft and rapid flow into inferior vena cava. Catheter was passed up right femoral vein into shunt, 75 ml bolus of dye was injected, and serial x-ray films were taken. Diameter and location of graft are well delineated along with prompt egress of dye into inferior vena cava. Shunt was inserted 3 years ago and patient has experienced no further bleeding.

cedure. All other grafts studied to date have remained patent, and the longest period of follow-up thus far has been 6 years.

The status of the graft has been studied in all patients who have died from their liver disease during the follow-up period. Ten such grafts have been studied and, with the exception of those listed above, all of these continue to show good patency with a smooth, glistening pseudointima on the inner surface of the graft.

Angiographic assessment of graft patency can be performed in a number of ways. The simplest technique involves retrograde catheterization of the shunt via the femoral vein and the vena cava (Fig. 19-9). After injection of a 50 ml bolus of contrast medium, sequential films are obtained by a rapid film changer. This technique has the advantage of permitting measurement of the superior mesenteric and portal venous pressures directly through the catheter. Transshunt pressures can also be obtained by continuous recording during withdrawal of the catheter across the shunt.

An alternative approach involves selective celiac and superior mesenteric arterial angiography to permit an accurate assessment of the arterial and venous flow dynamics in such patients. The patency of the graft can easily be shown by pressure injection of the contrast material into the superior mesenteric artery, obtaining sequential films during the venous phase. The dye in the inferior vena

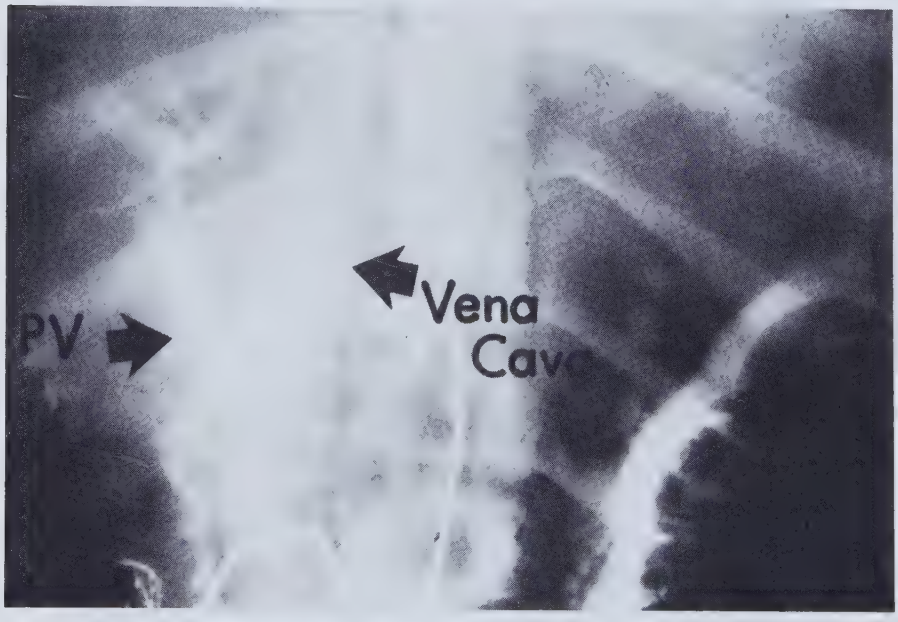

Fig. 19-10. Radiogram of portal venous system and vena cava following simultaneous injection of celiac axis and superior mesenteric artery with dye. In this particular patient there is not only patency of shunt but also continued perfusion of liver via portal vein from upper abdominal viscera. In this patient probably all of venous superior mesenteric flow is entering systemic circulation through shunt and flow from celiac circulation is perfusing liver. This type of observation has been documented in approximately one third of our patients.

cava can be readily identified. More importantly, injections of the celiac artery can also be performed in order to assess splenic and portal venous flow and to determine the presence or absence of prograde flow into the liver from the upper abdominal viscera (Fig. 19-10). In my experience, continued perfusion of the liver has been encountered in approximately one third of patients utilizing these techniques, because a definite correlation has been found between the preshunt pressures in these patients and the continued postoperative perfusion. In patients with high portal and intrahepatic sinusoidal pressure, it cannot be expected that perfusion of the liver will occur, because the perfusion pressure remaining in the superior mesenteric vein after the shunt procedure will not be sufficient to maintain portal perfusion. However, in my experience such patients have already adapted to diminished or even reversed portal flow, and the decompression of the hepatic parenchyma through the shunt may be necessary to prevent ascites, as previously mentioned.

Routine barium swallow x-ray examinations to document the disappearance of varices have also been performed in most patients. Varices may persist for as long as 6 months following the operative procedure, but in most instances they eventually disappear. Finally, the policy of readmittance at 6-month or 1-year intervals postoperatively has been established to document the patency of the grafts and to restudy the flow hemodynamics in the portal system as outlined.

ENCEPHALOPATHY

Hepatic encephalopathy has not been as great a problem in these patients to date as I have previously noted[8] and as noted by other investigators after portacaval shunts. Eight patients in the entire series (10%) presented with varying degrees of encephalopathy *prior* to the performance of a shunt, but this rapidly cleared with adequate preoperative preparation and correction of the secondary aldosteronism with spironolactone. Postoperative encephalopathy has been similarly encountered in these same patients. In two additional patients the encephalopathy was directly attributable to the injudicious use of diuretics by the patient's physician, resulting in severe potassium depletion and alkalosis. With careful monitoring of electrolyte status and the use of spironolactone, this problem has been avoided, and the overwhelming majority of the patients lead useful lives without the severe neurologic sequelae. Intermittent, mild encephalopathy, when present, has been easily controlled by a low-protein (30 gm) diet, potassium supplementation, and spironolactone. Antibiotic preparation of the colon has not been utilized in these patients.

The documentation of the high incidence, ranging from 20% to 50%, of postoperative hepatic encephalopathy after both the end-to-side and the side-to-side portacaval shunts as reported by McDermott,[18] Britton et al.,[4] Mikkelsen et al.,[21] Callow et al.,[5] and Warren et al.[35] would indicate that these patients are more apt to suffer from the ravages of encephalopathy than patients undergoing the more selective shunt procedures such as the distal splenorenal shunt, the proximal splenorenal shunt popularized by Linton,[13] and the interposition mesocaval shunt. Nevertheless, because encephalopathy occurs in patients with severe liver disease even without shunts, it is difficult to evaluate the contribution of the type of shunt to the development of hepatic encephalopathy post-

operatively. Warren et al.[35] have devised a procedure that electively decompresses the esophageal varices through the distal splenic vein via distal splenorenal shunt while at the same time permitting portal perfusion of the liver through the intact portal vein. Utilizing this operation, they have reported a very low incidence of hepatic encephalopathy in good-risk patients who have a high portal blood flow preoperatively. However, the concept of alteration of hepatic blood flow after shunt procedures as the cause of encephalopathy has been seriously questioned by Orloff[24] and Bismuth et al.,[3] who have found a lack of correlation between the incidence of encephalopathy and the amount of portal blood flow to the liver. In any case, the question remains unsettled at the present time.

The low incidence of encephalopathy in the patients in the study is similar to that reported by Linton utilizing the splenorenal shunt and is probably related to the fact that the interposition mesocaval shunt functions as a side-to-side shunt while at the same time leaving a higher portal pressure as a residual to permit perfusion of the liver in those patients who have a low preoperative sinusoidal pressure. Whether or not this is necessary remains controversial, but at least there does appear to be some preservation of the hepatic blood flow in those patients in whom sinusoidal resistance is sufficiently low to permit flow at this level of pressure.

The interposition mesocaval shunt acts as a "pop-off" valve because it provides decompression of the portal system, leaving a residual pressure in the portal system that may be sufficiently high to affect portal perfusion from the upper viscera or, alternatively, to decompress the hepatic parenchyma in those patients with reversed portal flow and high sinusoidal pressures.

It cannot be emphasized strongly enough that these patients must be followed carefully to avoid metabolic derangements such as the hyperkalemic alkalosis that is commonly encountered in patients with cirrhosis; they will need continuing care to avoid some of the metabolic complications that often are produced by the indiscriminate use of diuretics and other dietary controls.

LIFE SURVIVAL RATE ANALYSIS

Fig. 19-11 depicts the life survival rate analysis of the entire group of 80 patients. There was a 72% 5-year survival rate in these patients, and 15 patients have now survived 5 years or longer after the interposition mesocaval shunt procedure. This survival rate is extremely gratifying and a tribute not only to the type of shunt utilized but also to the excellent postoperative follow-up given to these patients by the house staff.

As might be expected, the survival rate is considerably better in the excellent-risk group A patient (Fig. 19-12). The figure quoted depicts a breakdown of the survival curves of patients, who are classified according to the criteria of Child. It can be seen that all of the patients who were group A risks continue to do well. Eighty-five percent of the group B patients and 65% of the group C patients are alive after 5 years. The lower survival of the last group is a result of the continued progression of the liver disease, because most of these patients have continued drinking, and deaths, when they have occurred, have been caused by liver failure and the continued deterioration of hepatic function.

More importantly, I believe that one of the advantages of this type of shunt is

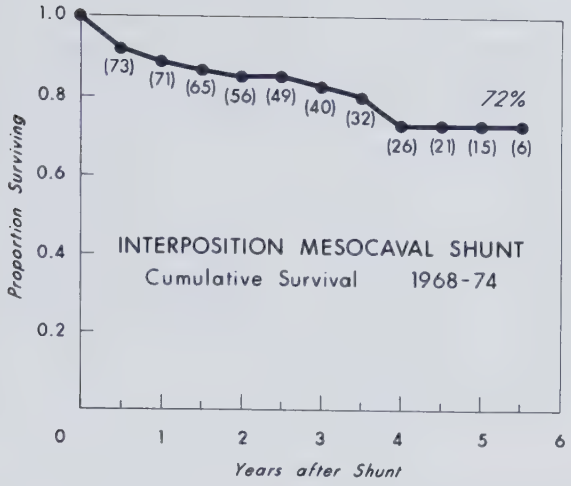

Fig. 19-11. Life survival analysis. (From Drapanas, T.: Ann. Surg. [In press.])

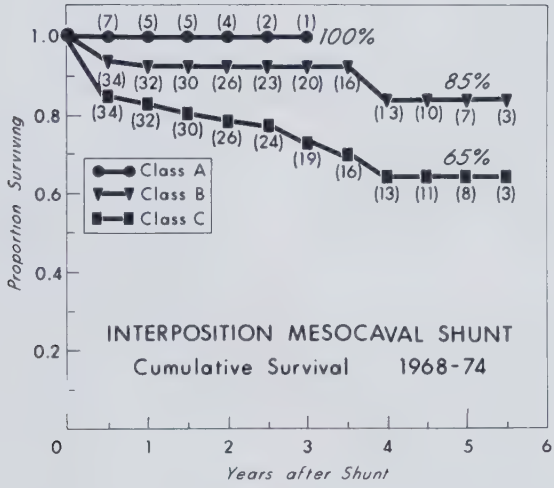

Fig. 19-12. Life survival analysis according to classification of severity of disease (Child's criteria). (From Drapanas, T.: Ann. Surg. [In press.])

the low (8%) operative mortality encountered to date. The more simple procedures in the poor-risk patient appear to be accompanied by a better result than the more complicated selective shunts that are difficult to perform, carry a higher operative mortality, and offer no advantage over this type of shunt. Indeed, Warren et al.[35] have indicated that the poor-risk patient with high sinusoidal pressure and ascites is not a candidate for the selective distal splenorenal shunt because of the high mortality they have encountered.

CONCLUSIONS

On the basis of my experience with the interposition mesocaval shunt over the past 6 years, this procedure has been found to be readily performed in the

average patient, to carry a low surgical mortality, and to be readily tolerated. Graft patency is extremely high, exceeding 95% during the period of follow-up in this group of patients. Analysis of life survival rate tables from the same group shows that these patients are well protected against further hemorrhage and recurrent ascites, and in most patients relief of hypersplenism also occurs.

I also believe that the relatively low incidence of encephalopathy encountered after the use of this shunt may be related to the continued perfusion of the liver in those patients in whom sinusoidal resistance within the liver is sufficiently low to permit blood flow from the upper abdominal viscera. The latter situation has been confirmed in approximately one third of the patients studied by careful angiographic assessment of the portal and superior mesenteric hemodynamics postoperatively.

Finally, I believe that this graft can be applied with good results in all patients who have a patent superior mesenteric vein.

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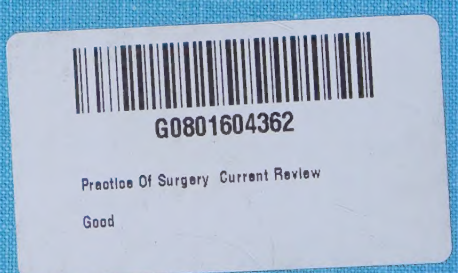
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